SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Prosthesis, Hip, Semi-constrained, Resurfacing Metal/Metal hybrid fixation

Device Trade Name: CONSERVE® Plus Total Resurfacing Hip System

Applicant's Name and Address: Wright Medical Technology, Inc.
5677 Airline Road
Arlington, TN 38002

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P030042

Date of FDA Notice of Approval: November 3, 2009

Expedited: Granted expedited review status on March 30, 2004 because total hip systems with a resurfacing femoral component and a metal-on-metal articulation may offer advantages in safety and effectiveness over existing alternatives; such as, the preservation of femoral bone stock during implantation as compared to metal-on-metal total hip systems and a decrease in adverse tissue reaction due to particulate wear debris as compared to metal-on-polyethylene resurfacing hip systems.

II. INDICATIONS FOR USE

The CONSERVE® Plus Total Resurfacing Hip System is a single use device intended for hybrid fixation utilizing: cemented femoral head component and cementless acetabular component. The CONSERVE® Plus Total Resurfacing Hip System is intended for use in resurfacing hip arthroplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients having the following conditions:

- Non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/developmental dislocation of the hip (DDH), or
- Inflammatory arthritis such as rheumatoid arthritis.

The CONSERVE® Plus Total Resurfacing Hip System is intended for patients who, due to their relatively younger age or increased activity level, may not be suitable for traditional total hip arthroplasty due to an increased possibility of requiring future ipsilateral hip joint revision.

III. CONTRAINDICATIONS

The CONSERVE® Plus Total Resurfacing Hip System should not be implanted in patients with the following conditions:

- Patients with active or suspected infection in or around the hip joint.
- Patients who are skeletally immature.
- Patients with bone stock inadequate to support the device including:
  - Patients with severe osteopenia should not receive the CONSERVE® Plus Total Resurfacing Hip procedure. Patients with a family history of severe osteoporosis or severe osteopenia;
  - Patients with osteonecrosis or avascular necrosis (AVN) with >50% involvement of the femoral head (regardless of FICAT Grade) should not receive a CONSERVE® Plus Total Resurfacing Hip System device; or
  - Patients with multiple cysts of the femoral head (>1cm) should not receive a CONSERVE® Plus Total Resurfacing Hip System device.

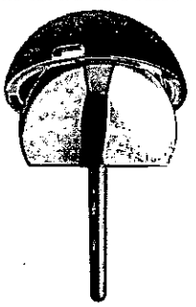
  NOTE: In cases of questionable bone stock, a Dual-Energy X-ray Absorptiometry (DEXA) scan may be necessary to assess inadequate bone stock.
- Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery.
- Females of child-bearing age due to unknown effects of metal ion release on the fetus.
- Patients with known moderate to severe renal insufficiency.
- Patients who are immunosuppressed with diseases such as AIDS or persons receiving high doses of corticosteroids.
- Patients who are obese and/or with a BMI>35.
- Patients with known or suspected metal sensitivity (e.g., jewelry).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CONSERVE® Plus Total Resurfacing Hip System labeling.

V. DEVICE DESCRIPTION

The CONSERVE® Plus Total Resurfacing Hip System is a metal-on-metal hip resurfacing system. The system is composed of a stemmed resurfacing femoral component for cemented fixation; and a one-piece acetabular shell for cementless, press-fit fixation. The device is a "resurfacing" hip system because only the surface of the femoral head is removed to implant the femoral component.



The design features of the CONSERVE® Plus Resurfacing Femoral Component are as follows:

- Manufactured from Cast Cobalt Chrome Alloy conforming to ASTM F75[1].
- Offered in a range of outer diameters from 36mm to 54mm in 2mm increments.
- The articulating surface of the implants is superfinished to insure form tolerance and a fine surface finish.
- The undersurface of the femoral component has a "glass-bead" blasted surface finish (125 Ra Max) and contains a shallow circumferential undercut band at the head's equator.
- A tapered stem geometry.

The design features of the CONSERVE® Plus Acetabular Shells are summarized below:

- Manufactured from Cast Cobalt Chrome Alloy conforming to ASTM F75.
- Porous coated with Cobalt Chrome Alloy sintered beads conforming to ASTM F1377.
- The articulating surface of the implants is superfinished to insure form tolerance and a fine surface finish.
- Available Sizes: 36mm ID/46mm OD to 54mm ID/64mm OD in 2mm increments.

Sizing and System Compatibility

The correct selection of the prosthesis is extremely important. The potential for success in total hip resurfacing arthroplasty is increased by selection of the proper size of the prosthesis. Total hip resurfacing prostheses require careful seating and adequate bone support.

The femoral heads are compatible with the following acetabular components:

CONSERVE® Plus Total Resurfacing Hip System Sizing and System Compatibility	
Femoral Component (Nominal Outer Diameter)	Acetabular Component (Nominal Inner Diameter/ Nominal Outer Diameter of shell)
36mm	36mm ID/ 46mm OD
38mm	38mm ID/ 48mm OD
40mm	40mm ID/ 50mm OD
42mm	42mm ID/ 52mm OD
44mm	44mm ID/ 54mm OD
46mm	46mm ID/ 56mm OD
48mm	48mm ID/ 58mm OD
50mm	50mm ID/ 60mm OD
52mm	52mm ID/ 62mm OD
54mm	54mm ID/ 64mm OD

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the reduction or relief of pain and/or improved hip function including:

- Non-surgical treatment (e.g., reduced activity, medications, physical therapy) or no treatment at all;
- Other commercially available total hip replacement devices. Commonly used implant bearing materials for total hip arthroplasty include metal on ultra-high molecular weight polyethylene (UHMWPE), ceramic on UHMWPE, metal on metal, and ceramic on ceramic. Total hip replacement devices are implanted by either cemented or uncemented techniques;

- Other commercially available total hip resurfacing devices, which consist of metal on metal bearings;
- Rotational osteotomy; and
- Hip fusion.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CONSERVE® Plus Total Resurfacing Hip System has been marketed in the European Union since 2001. It has also been distributed in the countries listed below. The CONSERVE® Plus Total Resurfacing Hip System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

Worldwide Marketing History	
Argentina	Jamaica
Australia	Japan
Brazil	Russia
Canada	South Africa
Chile	South Korea
China	Taiwan
Colombia	Turkey
Egypt	United Arab Emirates

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Reported Device Related Adverse Effects
The most commonly reported adverse events related to the CONSERVE® Plus Total Resurfacing Hip System device are:

- Femoral neck fracture,
- Component migration/loosening,
- Femoral subsidence,
- Dislocation,
- Infection,
- Impingement, and
- Trochanteric fracture.

For the specific adverse events that occurred in the clinical studies, please see the Summary of Clinical Study section (Section X) below.

Potential Adverse Effects

The following adverse effects may occur in association with hip replacement surgery, including the CONSERVE® Plus Total Resurfacing Hip System:

- Device failure because the components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone.
- Surgical complications including, but not limited to: genitourinary disorders; gastrointestinal disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction or death.
- Sudden, pronounced, intraoperative blood pressure decrease due to the use of bone cement.
- Hematoma or damage to blood vessels resulting in large blood loss.
- Delayed wound healing.
- Superficial or deep infection. Infections may occur months to years after surgery. These infections are difficult to treat and may require reoperation with removal surgery and replacement at a later time.
- Temporary or permanent nerve damage resulting in pain or numbness of the affected limb.
- Metal sensitivity reactions, allergic reactions, or metallosis.
- Dislocation and subluxation leading to postoperative joint instability (which may be caused by malpositioning of the implants or muscle / fibrous tissue laxity).
- Loosening of hip resurfacing components can occur. Early mechanical loosening may result from inadequate initial fixation, malalignment, latent infection, premature loading of the prosthesis, or trauma. Late loosening may result from trauma, infection, biological complications (including osteolysis), or mechanical problems, with the subsequent possibility of bone erosion and/or pain.
- Limb length discrepancy.
- Device related noise such as, clicking, popping, squeaking or grinding.
- Increased hip pain and/or reduced hip function.
- Fatigue fracture of the implants as a result of excessive loading, malalignment, or trauma.
- Osteolysis and/or other peri-prosthetic bone loss.
- Bone perforation or fracture (occurring either intra-operatively or occurring post-operatively as a result of trauma, excessive loading, osteolysis or osteoporosis).
- Periarticular calcification or ossification.
- Wear and deformation of the articular surface (as a result of excessive loading or implant malalignment).
- Pseudotumor.
- Aseptic Lymphocyte Dominated Vasculitis Associated Lesion (ALVAL).

Any of these adverse effects may require medical or surgical intervention. In rare cases, these adverse effects may lead to death. The potential long-term biological effects of metal wear debris and metal ion production are not known.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Non clinical laboratory information was provided in support of the CONSERVE® Plus Total Resurfacing Hip System including the information regarding:

- Femoral Resurfacing Component: stem static and fatigue strength;

- Acetabular Shell: impaction and fatigue strength, surface coating parameters;
- Bearing Couple: wear, frictional torque, and range of motion; and
- Sterilization and Shelf-Life Validation

1. Femoral Resurfacing Component

The static and fatigue strength of the CONSERVE® Plus Total Resurfacing Hip System Femoral Component stem were evaluated.

Femoral Stem Static and Fatigue Strength

Worst case
The articulating surface of the test component was fixed and a cantilever load was applied to the distal tip of the femoral stem. Therefore, the component with the longest stem (56mm) was chosen as the worst case device.

Acceptance Criteria
The test components should survive 5 Million Cycles of fatigue loading at 267N (approximately 50% of the static failure load).

Methods
The articulating surface of the femoral component was fixed and a static load was applied to the distal tip of the stem until the material yielded and plastic deformation began. The maximum static load was recorded. Six samples were then dynamically tested at 267 N (approximately 50% of the static failure load) at 10Hz to five million cycles.

Results
The mean static failure load was 534 N. Six samples were then dynamically tested at 267 N at 10Hz to five million cycles without failure in the same test configuration. The results of these static and dynamic tests demonstrate that the femoral stem should withstand predicted *in vivo* loads.

2. Acetabular Shell

The impaction and fatigue strength and surface coating parameters of the CONSERVE® Plus Total Resurfacing Hip System Acetabular Shells were evaluated.

Impaction Testing

Worst Case Design
Impaction testing was conducted on the CONSERVE® Plus Acetabular Shell to ensure that deformation upon impaction would not significantly impact articulation and clearance between the femoral and acetabular components. For this test configuration, worst case is determined by the thinnest wall thickness.

Acceptance Criteria
The deformation of the CONSERVE® Plus Acetabular Shell with a 5mm wall thickness should not significantly impact articulation and clearance between the femoral and acetabular components.

Methods
The ultimate compressive strength of the underlying structure (cortical bone) is most critical during impaction and torque testing. ULTEM™ 1000 was chosen to simulate cortical bone because its ultimate compressive strength most closely resemble cortical bone material properties (Cortical Bone= 155-163 MPa; ULTEM™ 1000= 150 MPa).

The impaction/torque studies are more severe than any typical in-vivo condition since they assume that the entire acetabulum consists of the cortical bone. However, they can have some merit as the "absolute worst case implantation" condition. The dimensional changes identified in the impaction/torque study could affect the clearances between the femoral component and the various acetabular shell designs. The Conserve® Plus Acetabular shells were impacted into ULTEM 1000 with a 1mm press-fit, per the recommended surgical technique.

Results
The results of this study showed that the CONSERVE® Plus shell with a 5mm wall thickness had an average change in the inner diameter of 7 +/- 4μm after impaction with a 1mm press-fit. The result of the impaction testing demonstrates that the acetabular shell deformation should not significantly affect articulation or clearance between femoral and acetabular components.

Fatigue Strength Testing

Worst Case Design
The worst case design option chosen for testing was a shell with a constant 3mm wall thickness. Although this shell successfully passed fatigue testing, it was not chosen as the final CONSERVE® Plus Acetabular Shell to be marketed because of its performance in other testing. However, because it was thinner than the 5mm Conserve® Plus Acetabular Shell, the fatigue testing of this component was considered a worst-case design and was used as validation for the CONSERVE® Plus Acetabular Shell to be marketed.

Acceptance Criteria
The shells should complete 5 million cycles at a peak load of 2500N without evidence of shell fracture.

Methods
The acetabular shells were placed in support rings that provided a 3mm band of support around the rim of the shell. An MTS 858 Bionix biaxial servohydraulic test frame was used to apply a cyclic load of 250N-2500N through the femoral head to six components to represent typical compressive loading in the hip. The components were tested for 5 million cycles at 30 Hz.

Results
All six components completed 5 million cycles of loading without any evidence of shell fractures. The result of the dynamic fatigue test demonstrates that the acetabular shell deformation should withstand predicted *in vivo* loads.

Surface Coating Characterization

Worst Case Design
The CONSERVE® Plus Acetabular Shells are coated with Cobalt Chrome sintered beads.

Acceptance Criteria
The criteria for porous-coated components are described in FDA's *Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement*[2], dated April 28, 1994.

Methods
The porous coating was characterized with regard to coating thickness, bead morphology, pore size, porosity, and bond strength characteristics.

Results
The results of the porous coating characterization are summarized in Table A below. The results demonstrate that the Conserve® Plus Acetabular Shell coating thickness, pore size, porosity, and structure (interconnecting porosity) meet the definition of a porous-coating.

Table A: Porous Coating Characterization

Mean Coating Thickness	0.854 mm
Bead Shape	Spherical Powder
Average Bead Size	0.278 mm
Mean Pore Size	145 µm
Mean Volume Percent Porosity	34.20%
Mean Shear Strength	5819 psi
Mean Tensile Pull-off Strength	7808 psi

3. Bearing Couple

The wear rate, frictional torque, and range of motion of the CONSERVE® Plus Total Resurfacing Hip System were evaluated.

Wear Testing

Worst Case Design
The 54mm bearing size is expected to be the worst case component tested. A mid-range size (44mm) was also tested.

Acceptance Criteria
The amount of wear was compared to results reported in the published literature for other total hip replacement bearings.

Methods

Twelve (12) 44mm bearings and four (4) 54mm bearings were tested for 5 million cycles in Shore Western Hip Simulators using bovine serum as the lubricant. The test was interrupted at regular intervals throughout the process for gravimetric assessment of the bearing wear. The gravimetric wear data was then converted into volumetric wear data that is shown in Table B.

Results

Results of the wear tests referenced above are summarized in Table B below.

Table B: CONSERVE® Plus Wear Rates

	Run-in wear rate @ 0.5 million cycles* (mm^3/million cycles)	Run-in wear rate @ 2 million cycles* (mm^3/million cycles)	Steady-state wear rate (mm^3/million cycles)	Total wear, 5 million cycles (mm^3)**
44mm Bearing Couple, 5mm wall	2.462	---	0.084	1.610
54mm Bearing Couple, 3 mm wall	---	.956	.145	2.345

Notes:

*The run-in wear period for the 44mm testing was 0.5 million cycles while the run-in period for the 54 mm testing was 2 million cycles.

**The total wear for 5 million cycles is calculated by the following equation: (run-in wear rate) x (run-in wear period) + (steady-state wear rate) x (steady-state wear period) = total wear.
For the 44mm couple, total wear was (2.462 x 0.5) + (0.084 x 4.5) = 1.610
For the 54 mm couple, total wear was (0.956 x 2.0) + (0.145 x 3.0) = 2.345.

Both the 44mm and 54mm CONSERVE® Plus Total Resurfacing Hip System couples showed wear rates that are similar to results reported in published literature for other total hip replacement bearings.

Frictional Torque Testing

Worst Case Design

Since torque is proportional to head size, the 54mm bearing size is considered to be the worst case components tested.

Acceptance Criteria

The torque generated by the bearing couple was compared to the results reported in the published literature for other total hip replacement bearings.

Methods

Evaluated the frictional torque generated by 6 CONSERVE® Plus 54mm bearing size Couples. The frictional torque was recorded for each bearing couple in flexion-extension and internal-external rotation under a joint load of 2300N, using an MTS Bionix 858 test system.

Results

Results of the frictional torque tests referenced above are summarized in Table C below.

Table C: Average Frictional Torque After Simulated Impaction

Bearing Description	Flexion-Extension Frictional Torque (N-m)	Internal-External Rotation Frictional Torque (N-m)
CONSERVE® Plus Bearing Couple (5mm thick shell)	6.21	1.79

All measured frictional torque values for the CONSERVE® Plus Total Resurfacing Hip System similar to results reported in the published literature for other total hip replacement bearings.

Range of Motion

Worst Case Design
A cylindrical "femoral neck" was utilized to detect impingement between the acetabular cup and femoral neck of a 56mm CONSERVE® Plus Femoral Resurfacing Component. Although the largest femoral resurfacing component available is 54mm, a 56mm component was used and results in a worst case range of motion as compared to the 54mm component. A cylindrical "femoral neck" was used as it results in the smallest angle of articulation.

Acceptance Criteria
As outlined in ISO 21535 "Specific Requirements for Hip-joint Replacement Implants"[3] the minimum allowable angle of flexion/extension is 80°, abduction/adduction is 60° and internal/external rotation is 90°.

Method
Range of motion was evaluated using CAD models following a procedure that is based on that which is outlined in ISO 21535. The test protocol was modified to consider the bone conserving nature of hip resurfacing by adding a cylindrical femoral neck to simulate the worst case amount of bone possible. Range of Motion was determined by identifying the angle at which impingement occurs in the CAD models.

Results
The worst case flexion/extension and abduction/adduction angle at which impingement occurred was 80°. The worst case internal/external degree of rotation at which impingement occurred was 128°. These values meet the minimum requirements specified in ISO 21535.

4. Sterilization and Shelf-Life Validation

Femoral head and acetabular components of the CONSERVE® Plus Total Resurfacing Hip System are sterilized by gamma irradiation. The sterilization process has been validated to achieve a sterility assurance level of 10^{-6} at a minimum dose of 25kGy in compliance with the requirements of ISO 11137 "Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization."[4] The product is not labeled "pyrogen free". The components are packaged in

Tyvek® and thermoformed trays to maintain sterility. Shelf life testing was performed to verify sterile packaging integrity equivalent to eight years.

5. Biocompatibility

Because the device is comprised of well-accepted materials for permanent implant (i.e., materials conforming to ASTM F75[1] and F1377[5]), additional biocompatibility testing was not required.

Laboratory Studies Conclusion

CDRH determined that the preclinical mechanical bench testing provides a reasonable assurance of device safety.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of total resurfacing arthroplasty with the CONSERVE® Plus Total Resurfacing Hip System for the above stated indications for use in the US under IDE # G990328. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Purpose of the Investigation

The purpose of this investigation was to test the hypothesis that the CONSERVE® Plus Total Resurfacing Hip System is as safe and effective as conventional total hip arthroplasty. The CONSERVE® Plus Total Resurfacing Hip System (CONSERVE® Plus) was the investigational treatment and the TRANSCEND® Ceramic Total Hip Arthroplasty System (TRANSCEND® Ceramic) and the TRANSCEND® Metal Total Hip Arthroplasty System (TRANSCEND® Metal) served as the control groups. Safety was determined by collection of the incidence of peri-operative and post-operative complications, revisions, and device related adverse events. Effectiveness was measured via a Composite Clinical Success endpoint that included an evaluation of pain and function using the Harris Hip Score (HHS), patient self-evaluation of health related quality of life which included physical and metal-health components (SF-12), radiographic data, and survivorship as described below.

B. Study Design

A prospective, multi-center, historically controlled Investigational Device Exemption (IDE) study was conducted using components of the CONSERVE® Plus Total Resurfacing Hip System in the United States. *A priori* objectives were used to demonstrate non-inferiority to historical control groups in terms of a composite clinical success (CCS) criterion, evaluated at Month 24 or later. The historical control groups were derived from the regulatory studies for the TRANSCEND® Ceramic IDE and the TRANSCEND® Metal IDE. The database for this PMA reflected third-party audited data collected through November 20, 2006.

The following table (Table 1) provides a comparison of the investigational and control group study parameters.

Table 1: Comparisons of Investigational and Control Group Study Parameters

Protocol Element	CONSERVE® Plus (I)	Ceramic TRANSCEND (C1)	Metal TRANSCEND (C2)
Type of Study	IDE Hip Resurfacing	IDE Total Hip Arthroplasty	IDE Total Hip Arthroplasty
Bearing Type	Metal on Metal	Ceramic on Ceramic	Metal on Metal
Study Design	Prospective, non-randomized, historical control	Prospective, non-randomized, historical control	Prospective, non-randomized, historical control
Number of Centers	11	10	19
Dates of First Enrollment	29-Aug-2000	7-Apr-1997	15-Sep-1997
Dates of Last Enrollment	25-May-2006	12-Jun-2001	23-Jul-2001
Number of Procedures	1366 All Enrolled-Audited 292 Pivotal Unilateral Efficacy Cohort (Original Shell) 680 All Enrolled Unilateral (Original Shell) Cohort 203 Bilateral Cohort (Original Shell)	963 All Enrolled 341 Pivotal Unilateral Efficacy Cohort 668 Complete Follow-up Safety Cohort 255 Bilateral Cohort	388 All Enrolled 322 Pivotal Unilateral Efficacy Cohort 345 Complete Follow-up Safety Cohort 64 Bilateral Cohort
Follow-up Intervals	Preoperative Operative 6 month 12 month 24 month 24+ Month	Preoperative Operative 6 month 12 month 24 month 24+ Month	Preoperative Operative 6 month 12 month 24 month 24+ Month
Outcome Measures	Harris Hip Score SF-12 Radiographic Evaluation Adverse Event Reporting	Harris Hip Score SF-12 Radiographic Evaluation Adverse Event Reporting	Harris Hip Score SF-12 Radiographic Evaluation Adverse Event Reporting

Note: For the purpose of including available data beyond the Month 24 window, a 24+ Month interval was created. The 24+ month evaluations include 24 month evaluations completed, as well as data from a later visit, if the 24 month evaluation was not available.

1. Study Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the inclusion/exclusion criteria. Table 2 lists the inclusion/exclusion criteria of the studies in which clinical data was collected for Groups I (CONSERVE® Plus), C1 (TRANSCEND® Ceramic) and C2 (TRANSCEND® Metal). If a criterion in Group I was identical to criteria in Groups C1 and/or C2, "identical criterion" is indicated. Where a criterion in a Group was not included in one or more of the other Groups "criterion not specified in protocol" is stated.

Table 2: Inclusion / Exclusion Criteria for Studies on Groups I, C1 and C2

INCLUSION CRITERIA		
Group I	**Group C1**	**Group C2**
Primary hip surgery for Noninflammatory Degenerative Joint Disease (NIDJD) such as osteo/degenerative arthritis, traumatic arthritis, congenital hip dysplasia, and avascular necrosis.	Identical Criterion	Identical Criterion
Primary hip surgery for Inflammatory Degenerative Joint Disease (Rheumatoid arthritis)	Criterion not specified in protocol	Criterion not specified in protocol
Skeletally mature or at least 18 years of age.	Skeletally mature and 21 years of age or older.	Identical Criterion
Signs the Informed Consent form.	Identical Criterion	Identical Criterion
Already enrolled in the study and present with a need for revision of either or both resurfacing components. These patients may have the failed component(s) revised with an investigational(s) component.	Already enrolled into the study and present with a need for revision may have the failed component revised with an investigational component as long as all components including the shell and femoral stem are revised. Revision of ceramic components only is not allowed.	Already enrolled into the study and present with a need for revision of the metal liner/acetabular shell component or present with a need for revision of the metal head/femoral stem component may have the failed component revised with an investigational component.

EXCLUSION CRITERIA		
Group I	**Group C1**	**Group C2**
Previous fusion, acute femoral neck fracture and/or above knee amputation.	Criterion not specified in protocol	Criterion not specified in protocol
Active infection.	Identical Criterion	Identical Criterion
Pregnant.	Pregnant or whose pregnancy status is unknown.	Pregnant or whose pregnancy status is unknown.
Neurologic or musculoskeletal disease that may adversely affect gait or weight-bearing.	Identical Criterion	Identical Criterion
Previously undergone an ipsilateral hemi resurfacing, total resurfacing, total bipolar, unipolar or total hip replacement device.	Previously undergone a total bipolar or unipolar hip replacement device.	Previously undergone a total bipolar or unipolar hip replacement device.
Active hepatitis or HIV infection.	Identical Criterion	Identical Criterion
Prisoners.	Identical Criterion	Identical Criterion
Body Mass Index (BMI) of >35.	Three times normal body weight.	Three times normal body weight.
Neuropathic joints.	Identical Criterion	Identical Criterion
Severe documented psychiatric disease.	Criterion not specified in protocol	Severe documented psychiatric disease.
Require structural bone grafts.	Criterion not specified in protocol	Criterion not specified in protocol
Documented allergy to cobalt chromium molybdenum.	Criterion not specified in protocol	Criterion not specified in protocol
Ipsilateral girdlestone.	Criterion not specified in protocol	Criterion not specified in protocol
Sickle cell disease or trait	Criterion not specified in protocol	Criterion not specified in protocol
Significant femoral head or neck deformity or significant acetabular wall deficiency.	Criterion not specified in protocol	Criterion not specified in protocol
Criterion not specified in protocol	Criterion not specified in protocol	Diagnosed with osteoporosis.
Criterion not specified in protocol	Criterion not specified in protocol	History of malignancy.

2. Follow-up Schedule

The follow-up time points and the intervals around these time points were analyzed in the same manner. Identified below are the follow-up time points and the corresponding intervals used

within the study which are based on the number of days after the operative procedure (Table 3). For the purpose of including available data beyond the Month 24 window, when the Month 24 data was missing, a 24+ Month interval was created. The 24+ month evaluations include 24 month evaluations completed, as well as data from a later visit, if the 24 month evaluation was not available. As noted in Table 3, different intervals were used to analyze the data.

Table 3: Study Intervals

	Actual (B) Extended Interval (Days)	Actual (A) FDA Guidance Interval[6] (Days)
Immediate	1-45	1-56
Month 6	46-210	168-196
Month 12	211-425	305-425
Month 24	426-790	670-790
Month 24 +	Any evaluation 22+ months = 24+	Any evaluation 22+ months = 24+

3. Clinical Endpoints

The safety of the CONSERVE® Plus Total Resurfacing Hip System was evaluated in terms of the following analyses:

- Device Revision,
- Risk Factors,
- Survivorship,
- Adverse Events, and
- Metal Ions.

Effectiveness was evaluated primarily by the Composite Clinical Success definition (immediately below). Harris Hip Score, radiographic outcome, and Health Related Quality of Life (SF-12) Scores were also evaluated as a measure of effectiveness.

With regards to success/failure criteria, a patient was defined as a success at the Month 24+ follow-up timepoint if all of the following Composite Clinical Success (CCS) Endpoints were met:

- No worse than 'mild' pain (Harris Hip Score item ≥ 30 points).
- Ability to walk at least '2 to 3 blocks' (Harris Hip Score item ≥ 5 points).
- Ability to climb stairs 'in any manner' (Harris Hip Score item ≥ 1 point).
- Ability to 'enter public transportation' (Harris Hip Score item = yes).
- Comfortable in a high chair for at least one-half hour (Harris Hip Score item ≥ 3 points).
- Putting on shoes and socks 'with ease' (Harris Hip Score item = 4 points).
- An overall Harris Hip Score ≥ 80 points.
- An increase in the Harris Hip Score of at least 15 points relative to baseline.
- A value for the total SF-12 score (sum of physical component score and mental-health component score) at least as large as the pre operative value.
- Absence of complete radiolucency, which was determined by independent radiographic evaluation of four views: acetabular AP view (3 regions), acetabular lateral view (3 regions), femoral stem

AP view (3 regions), and femoral stem lateral view (3 regions). Complete radiolucency in a view was defined to be present if there was any radiolucency of any size present in all zones comprising that view.

- Did not undergo revision, removal, or replacement of any component of the device up to that point in time.
- Did not experience a serious, device-related adverse event up to that point in time.

C. Study Population

Clinical study data was collected on 1851 hips implanted with the CONSERVE® Plus. A subset of the data was audited and these audited 1366 procedures (1206 patients) constitute the All Enrolled Audited cohort. Of these 1366 procedures, 680 were unilateral procedures implanted with the CONSERVE® Plus resurfacing femoral component and the original acetabular shell (described in the Device Description above) and were eligible, based on date of surgery, for the 24+ Month follow-up. There were 458 procedures within the 1366 procedure cohort that also received the CONSERVE® Plus resurfacing femoral component but a different version of the acetabular shell which is not included in this Summary. These procedures are included in the 1366 procedure cohort to provide a complete description of device safety.

Table 4 describes the various cohorts assessed in this clinical study. The core data collected from these cohorts was the same.

Table 4: Study Populations

COHORT	SAMPLE SIZES	DEFINITION
All Enrolled Audited	1366 procedures 1206 patients	This cohort has dates of surgery from 8/29/00 to 11/20/06. Data includes procedures implanted with resurfacing femoral component and either the original version of the acetabular shell (described in the Device Description above) or a different version of the acetabular shell which is not included in this Summary. Cohort used to provide supporting evidence of safety. All 1366 procedures were audited by a 3rd party.
Pivotal Unilateral Efficacy Cohort (Original Shell)	292 procedures 292 patients	This cohort has dates of surgery from 10/17/00 to 04/08/02. Includes unilateral non-inflammatory degenerative joint disease (NIDJD) procedures. Staged bilateral patients whose 24 month evaluation occurred prior to having the contralateral hip replacement are also included. Patients enrolled in separate training arm during this time period are not included. All patients in this cohort received the original version of the acetabular shell. Used to evaluate safety and efficacy and the Composite Clinical Success (CCS) definition to determine study success.
All Enrolled Unilateral (Original Shell)	680 procedures 680 patients	This cohort has dates of surgery from 8/28/00 to 01/19/06. This cohort includes all unilateral NIDJD procedures implanted after enrollment was completed for the Pivotal Unilateral Efficacy cohort; all unilateral rheumatoid arthritis procedures; all unilateral training arm procedures; and, were due, based on date of surgery, for Month 24 follow-up or later. All patients in this cohort received the original version of the acetabular shell. This cohort is used to provide supporting evidence of safety.
Bilateral Arm (Original Shell)	203 procedures 118 patients	This cohort has dates of surgery from 11/20/00 to 05/11/06. This cohort includes all patients implanted bilaterally (simultaneously or staged) prior to their Month 24 assessment. All patients in this cohort received the original version of the acetabular shell. This cohort is used to provide supporting evidence of safety.

Note: Due primarily to the fact that the All Enrolled Audited cohort contains 458 procedures implanted with a different version of the acetabular shell which is not included in this Summary, the Pivotal Unilateral Efficacy (Original Shell), All Enrolled Unilateral (Original Shell) and Bilateral Arm (Original Shell) cohorts, described in the above table, do not completely comprise the total 1366 procedures. The composition of the 1366 procedures in the All Enrolled Audited cohort is as follows: 292 Pivotal Unilateral Efficacy procedures, 656 Continued Access procedures, 318 Bilateral procedures, 35 Inflammatory Arm procedures, 8 Training Arm procedures and 57 procedures performed by a site whose data was excluded from the Pivotal Unilateral Efficacy cohort (Original Shell) due to audit findings.

D. Patient Accounting

The accounting of follow-up evaluations for the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) (Group I) and the control groups (C1 and C2) are provided in Table 5.

Table 5:
Procedure Accounting and Follow-up Compliance Table
Pivotal Unilateral Efficacy Cohort (Original Shell) (I), Ceramic THR Unilateral Controls (C1), Metal THR Unilateral Controls (C2)

As of Date of Database Closure	Pre-Op			Post-Op			Month 6			Month 12			Month 24			Month 24+		
	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2
(1) Theoretical follow-up	292	341	322	292	341	322	292	341	322	292	341	322	292	341	322	292	341	322
(2) Cumulative deaths including non-theoretically due	0	0	0	0	0	0	0	0	0	0	1	1	0	3	1	0	3	1
(3) Cumulative revisions including non-theoretically due	0	0	0	7	5	3	7	5	4	7	6	7	13	7	9	19	10	15
(4) Expected due for clinic visit	292	341	322	285	336	319	285	336	318	285	334	314	279	331	312	279	331	312
(5) Expected due + revisions among theoretically due	292	341	322	292	341	322	292	341	322	292	340	321	292	338	321	292	338	321
All Evaluated Accounting (Actual[B]) Among Expected Due Procedures																		
	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2
(6) Numbers of procedures with any clinical data in interval	291	341	322	232	220	237	238	261	294	248	258	229	235	208	208	268	280	276
(7) All Evaluated Visit Compliance (%)	99.7%	100.0%	100.0%	81.4%	65.5%	74.3%	83.5%	77.7%	92.5%	87.0%	77.2%	72.9%	84.2%	62.8%	66.7%	96.1%	84.6%	88.5%
(8) CCS at Mos. 24, 24+ or HHS+SF12+radio.	[redacted]			[redacted]			202	247	227	239	229	212	228	192	189	270	260	249
(9) Actual[B] % Follow-up for CCS or HHS+SF12+radio.							70.9%	73.5%	71.4%	83.9%	68.6%	67.5%	78.1%	56.8%	58.9%	92.5%	76.9%	77.6%
Within Window Accounting (Actual[A]) Among Expected Due																		
	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2
(10) CCS at Mos. 24, 24+ or HHS+SF12+radio	[redacted]			[redacted]			116	87	100	212	201	187	177	157	148	252	202	202
(11) Actual[A] % Follow-up for CCS or HHS+SF12+radio							40.7%	25.9%	31.4%	74.4%	60.2%	59.6%	60.6%	46.4%	46.1%	86.3%	59.8%	62.9%

Notes for Procedure Accounting and Follow-up Accounting Tables
ROM/Deformity Imputations - If post baseline Harris Hip Score evaluations were complete with the exception of ROM and Deformity, then ROM and/or Deformity were defined to be zero. This is a conservative imputation for both the primary CCS and secondary HHS efficacy criteria, since both require HHS to be equal to 80 points or greater and the maximum HHS score for this imputation can be 91, 95 or 96 points instead of 100 points (depending on whether ROM, Deformity or both were missing).
Actual[B] intervals: Immediate Post 1-45 days; 6 Mo. 46-210; 1 Yr. 211-425; 2 Yr. 426-790. For the purpose of including available data beyond the Month 24 window, a 24+ Month interval was created. The 24+ month evaluations include 24 month evaluations completed, as well as data from a later visit, if the 24 month evaluation was not available.
Actual[A] intervals: Immediate Post 1-56 days; 6 Mo. 168-196; 1 Yr. 305-425; 2 Yr. 670-790. For the purpose of including available data beyond the Month 24 window, a 24+ Month interval was created. The 24+ month evaluations include 24 month evaluations completed, as well as data from a later visit, if the 24 month evaluation was not available.
[1] The theoretical follow-up is the number of implants that would have been examined if all patients returned on the exact anniversary of their respective initial surgery dates.
[2] Cumulative deaths up to and including the current interval. Although the cumulative numbers of deaths are recorded on this row, only deaths among implants that are theoretically due for that interval are subtracted from theoretically due to determine the number expected due.
[3] This row records the cumulative number of failures that have taken place according by the exact anniversary of scheduled follow-up visit. Although the cumulative numbers of failures are recorded on this row, only failures among implants that are theoretically due for that interval are subtracted from theoretically due to determine the number expected due.
[4] Expected due for clinic visit is equal to theoretically due minus deaths and revisions among theoretically due . This row serves as denominator for clinical evaluation % followup.
[5] Expected due plus theoretically due revisions is computed by adding expected due to the number of cumulative revisions among theoretical procedures. This row serves as the denominator for composite clinical success (CCS) outcomes since revisions are known to be CCS failures.
[6] All Evaluated Accounting (Actual[B]) is based on the evaluations on-file among those expected due without regard to whether assessment was within the assessment window.
[7] All Evaluated Visit Compliance (%) is computed as the number on-file among those expected due divided by the expected number due expressed as a percentage. All evaluated compliance is based on the presence of any clinical data, even if incomplete, and demonstrates that the procedure is actively followed at least up to the specific interval.
[8] CCS at Mos. 24, 24+ or HHS+ change in SF12+radiographic, otherwise (Actual[B]). For Months 24 and 24+, this row indicates the numbers of procedures with all components on-file that are necessary to evaluate composite clinical success with revisions included as CCS failures. For other time points, this row only indicates that Harris Hip Total scores, change from baseline in SF12, and radiographic evaluations are on-file.
[9] Actual[B] % Follow-up for CCS or HHS+SF12+radio. This is the count of CCS procedures divided by the count of the expected due + revisions among theoretically due.
[10] CCS at Mos. 24, 24+ or HHS+change in SF12+radiographic, otherwise (Actual[A]). For Months 24 and 24+, this row indicates the numbers of procedures with all components on-file that are necessary to evaluate composite clinical success with revisions included as CCS failures. For other time points, this row only indicates that Harris Hip Total scores, change from baseline in SF12, and radiographic evaluations are on-file.
[11] Actual[A] % Follow-up for CCS or HHS+SF12+radio. This is the count of CCS procedures divided by the count of the expected due + revisions among theoretically due.

The following cohort follow-up rates are also noted:

All Enrolled Audited Cohort

The follow-up rate at Month 24+ for patients with complete information to determine safety was 76.4% (821/1074) for Group I, 60.4% (568/963) for Group C1, and 79.0% (305/386) for Group C2.

All Enrolled Unilateral (Original Shell) Cohort

The follow-up rate at Month 24+ for patients with complete information to determine safety was 81.2% (540/665).

Bilateral arm (Original Shell) Cohort

The follow-up rate at Month 24+ for patients with complete information to determine safety was 83.8% (160/191).

E. Baseline Characteristics of Investigational and Control Groups

The summary statistics / comparisons for patient demographics and baseline variables for the Pivotal Unilateral Efficacy (Original Shell), All Enrolled Audited, All Enrolled Unilateral (Original Shell), and Bilateral Arm (Original Shell) cohorts and the two historical controls are displayed in Tables 6 and 7 below.

Significantly different ($p<0.05$) preoperative demographic variables between the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) (Group I) and the TRANSCEND® Ceramic (Group C1) were gender, age, BMI, height in females, and preoperative mean Harris Hip total score. Harris Hip pain score was borderline significant ($p=0.052$). Significantly different ($p<0.05$) preoperative demographic variables between the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) and the TRANSCEND® Metal (Group C2) were gender, age, BMI, weight in males, and preoperative Harris Hip total and pain scores.

To assess any potential selection bias resulting from a non-randomized study design, a Propensity Score analysis and adjustment was performed. This analysis was performed separately for the CONSERVE® Plus cohort versus the TRANSCEND® Ceramic control and CONSERVE® Plus cohort versus the TRANSCEND® Metal control. The covariates entered into the propensity score adjustment were gender, age at surgery, BMI, diagnosis, baseline HHS, presence of marked pain at baseline, previous treatment, other joint involvement, and any bone graft used during the procedure, as these were the covariates believed to most affect outcome. The propensity score model estimated each subject's likelihood of receiving one device versus the other as a function of the covariates put in the model, thus determining whether the subjects were "exchangeable." The propensity scores were then put into quintiles and used to determine an adjusted odds ratio of being a Composite Clinical Success (CCS) in the CONSERVE® Plus cohort relative to each control group. This analysis showed that the likelihood of being a Month 24+ CCS was not significantly lower for patients in the CONSERVE® Plus cohort relative to each control group. This implies that any between group differences in patient populations for the covariates included in the model did not affect the conclusion of the non-inferiority analysis for CCS.

Table 6: Demographic Characteristics and Baseline Function in Pivotal Unilateral Efficacy Cohort (Original Shell) Patients and Unilateral Control Patients

	Pivotal Unilateral Efficacy Cohort (Original Shell) (I)		Ceramic THR Controls (C1)		Metal THR Controls (C2)		I vs. C1[1] p-values	I vs. C2[2] p-values
Number of procedures	292	.	341	.	322	.	.	.
Number of patients	292	.	341	.	322	.	.	.
Gender	**n**	**%**	**n**	**%**	**n**	**%**	0.046	0.046
Males	202	69.2%	210	61.6%	198	61.5%	.	.
Females	90	30.8%	131	38.4%	124	38.5%	.	.
Age	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	<0.001	<0.001
≥65	13	4.5%	65	19.1%	66	20.5%	.	.
<65	279	95.5%	276	80.9%	256	79.5%	.	.
Males	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age at surgery (yrs)	48.8	9.6	52.5	11.5	53.3	11.9	<0.001	<0.001
Body Mass Index (kg/m^2)	28.1	4.3	29.6	5.8	30.1	6.0	0.020	0.001
Height (inches)	70.3	3.0	69.7	3.3	70.2	3.3	0.433	0.776
Weight (lbs)	197.8	32.9	204.2	40.2	210.8	42.9	0.171	0.002
Females	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age at surgery (yrs)	48.9	8.9	53.3	13.0	53.7	11.7	0.006	0.001
Body Mass Index (kg/m^2)	27.1	6.1	29.3	8.1	29.0	7.3	0.038	0.050
Height (inches)	65.1	2.9	64.2	3.5	64.4	3.1	0.035	0.125
Weight (lbs)	163.1	37.2	171.1	43.2	171.0	43.2	0.251	0.281
Diagnosis	**n**	**%**	**n**	**%**	**n**	**%**	0.157[4]	0.363[4]
Osteo/degenerative arthritis	230	78.8%	243	71.3%	243	75.5%	.	.
Avascular necrosis	34	11.6%	58	17.0%	53	16.5%	.	.
Traumatic arthritis	13	4.5%	21	6.2%	13	4.0%	.	.
Congenital hip dysplasia	15	5.1%	19	5.6%	13	4.0%	.	.
Rheumatoid Arthritis	0	0.0%	0	0.0%	0	0.0%	.	.
Health Related Quality of Life (SF-12)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
SF-12 PCS Z-score[3]	-1.82	1.19	-1.88	1.09	-1.85	1.18	0.991	0.924
SF-12 MCS Z-score[3]	0.00	1.16	0.05	1.18	-0.01	1.10	0.877	0.365
Harris Hip Score	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Harris Hip Total Score	49.4	11.7	45.3	12.8	47.6	14.2	<0.0001	0.026
Harris Pain Category[6]	**n**	**%**	**n**	**%**	**n**	**%**	0.052[5]	<0.0001[5]
None/Ignores	0	0.0%	1	0.3%	5	1.6%	.	.
Slight	0	0.0%	2	0.6%	10	3.1%	.	.
Mild	5	1.7%	9	2.6%	11	3.4%	.	.
Moderate	105	36.1%	88	25.8%	90	28.0%	.	.
Marked	175	60.1%	229	67.2%	185	57.6%	.	.
Totally disabled	6	2.1%	12	3.5%	20	6.2%	.	.
	n	**%**	**n**	**%**	**n**	**%**		
Any Previous Treatment	45	15.4%	58	17.0%	46	14.3%	0.587	0.695
Other Joint Involvement	75	25.7%	70	20.5%	86	26.7%	0.124	0.773
Any bone graft	63	21.6%	85	24.9%	77	23.9%	0.321	0.491

Notes:
[1] I vs. C1 is Pivotal Unilateral Efficacy Cohort (Original Shell) vs. Ceramic THR controls: For interval variables, p-values are from ANOVA pairwise contrasts; for nominal variables, p-values are from pairwise chi-square statistics; for Harris Hip Total, p-values are from pairwise Wilcoxon rank sum tests.
[2] I vs. C2 is Pivotal Unilateral Efficacy Cohort (Original Shell) vs. Metal THR controls: For interval variables, p-values are from ANOVA pairwise contrasts; for nominal variables, p-values are from pairwise chi-square statistics; for Harris Hip Total, p-values are from pairwise Wilcoxon rank sum tests.
[3] SF-12 PCS and MCS Z-scores are age-adjusted and based on US national reference values.
[4] A 2 X 5 Chi square test was performed for Diagnosis versus controls
[5] A 2 X 6 Chi square test was performed for the Harris Hip Score Pain Category versus controls.
[6] One patient was missing pain assessment in baseline Harris Hip Score.

Table 7: Baseline and Demographic Characteristics for All Enrolled Unilateral (Original Shell), Bilateral (Original Shell), and All Enrolled Audited Cohorts

	All Enrolled Unilateral (Original Shell) n = 680		Bilateral (Original Shell) n = 203		All Enrolled Audited n = 1366	
	N	%	N	%	N	%
Number of procedures	680		203		1366	
Number of patients	680		118		1206	
Gender	**N**	**%**	**N**	**%**	**N**	**%**
Males	484	71.2%	153	75.4%	981	71.8%
Females	196	28.8%	50	24.6%	385	28.2%
Age	**n**	**%**	**n**	**%**	**n**	**%**
≥65	42	6.2%	11	5.4%	104	7.6%
<65	638	93.8%	192	94.6%	1262	92.4%
Males	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at surgery (yrs)	50.1	9.9	49.1	10.0	50.3	9.9
Body Mass Index (kg/m^2)	28.1	4.2	27.4	3.7	28.0	3.9
Height (inches)	70.4	2.7	70.7	3.0	70.6	2.8
Weight (lbs)	198.6	32.9	195.7	32.4	198.3	32.0
Females	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at surgery (yrs)	48.7	10.1	45.3	8.5	49.6	10.7
Body Mass Index (kg/m^2)	26.2	5.3	27.3	6.5	26.4	5.4
Height (inches)	64.9	2.8	65.6	3.6	65.2	3.0
Weight (lbs)	157.2	33.6	166	37.2	159.8	34.1
Diagnosis	**n**	**%**	**n**	**%**	**n**	**%**
Osteo/degenerative arthritis	519	76.3%	159	78.3%	1054	77.2%
Avascular necrosis	70	10.3%	28	13.8%	138	10.1%
Traumatic arthritis	31	4.6%	0	0.0%	39	2.9%
Congenital hip dysplasia	41	6.0%	16	7.9%	100	7.3%
Rheumatoid Arthritis	19	2.8%	0	0.0%	35	2.6%
Health Related Quality of Life (SF-12)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
SF-12 PCS Z-score	-1.88	1.16	-2.21	1.22	-1.92	1.16
SF-12 MCS Z-score	0.15	1.10	0.22	1.13	0.20	1.10
Harris Hip Score	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Total Score	50.6	12.0	49.6	12.9	50.7	11.9
Harris Pain Category[1]	**n**	**%**	**n**	**%**	**n**	**%**
None/Ignores	1	0.1%	1	0.5%	2	0.1%
Slight	5	0.7%	1	0.5%	7	0.5%
Mild	12	1.8%	8	4.0%	36	2.6%
Moderate	267	39.4%	70	34.7%	507	37.2%
Marked	377	55.6%	112	55.4%	781	57.3%
Totally disabled	16	2.4%	10	5.0%	29	2.1%
Any Previous Treatment	96	14.1%	10	4.9%	167	12.2%
Other Joint Involvement	172	25.3%	170	83.7%	550	40.3%
Any bone graft	164	24.1%	35	17.2%	281	20.6%

Note:
[1] Two patients were missing pain assessment in baseline Harris Hip Score.

F. Safety and Effectiveness Results

1. Safety Results

The safety of the CONSERVE® Plus Total Resurfacing Hip System was evaluated in terms of the following analyses:

- Device Revision,
- Risk Factors,
- Survivorship
- Adverse Events, and
- Metal Ions.

The risk analysis section identifies the factors which were shown to contribute to revision. Survivorship analyses were conducted according to the Kaplan-Meier approach.

Device Revision

There were a total of 66 (8.0%) revisions reported out of 821 procedures in the CONSERVE® Plus Total Resurfacing Hip System All Enrolled Audited cohort, 36 (6.7%) revisions reported out of 540 procedures in the All Enrolled Unilateral (Original Shell) cohort, 19 (7.0%) revisions reported out of 270 in the Primary Unilateral Efficacy cohort (Original Shell), and 11 (6.9%) revisions out of 160 in the Bilateral (Original Shell) cohort at the 24+ Month interval. A summary of the reason for revision, stratified by study cohort, is provided in Table 8 below.

Table 8:
All Revisions/Removals Reported By Cohort for the 24+ Month Interval

	All Enrolled Audited (N=1366) (24+ Month N = 821)			All Enrolled Unilateral (Original Shell) (N=680) (24+ Month N = 540)			Pivotal Unilateral Efficacy Cohort (Original Shell) (N=292) (24+ Month N = 270)			Bilateral Cohort (Original Shell) (N=203) (24+ Month N = 160)		
	n/N	%	Mean # Months	n/N	%	Mean # Months	n/N	%	Mean # Months	n/N	%	Mean # Months
Revision	66/821	8.0%	18	36/540	6.7%	19	19/270	7.0%	22	11/160	6.9%	29
Acetabular Loosening	10	1.2%	16	3	0.6%	31	3	1.1%	31	1	0.6%	10
Acetabular Migration	4	0.5%	9	1	0.2%	16	0	0.0%	N/A	0	0.0%	N/A
Acetabular Protrusion	1	0.1%	31	1	0.2%	31	0	0.0%	N/A	0	0.0%	N/A
Acetaular Loosening & Femoral Neck Fracture	1	0.1%	52	0	0.0%	N/A	0	0.0%	N/A	1	0.6%	52
Femoral Loosening	7	0.9%	36	3	0.6%	23	1	0.4%	19	4	2.5%	46
Femoral Neck Fracture	28	3.4%	11	19	3.5%	12	11	4.1%	16	4	2.5%	13
Impingement	2	0.2%	54	2	0.4%	54	1	0.4%	69	0	0.0%	N/A
Infection	8	1.0%	14	4	0.7%	15	2	0.7%	21	1	0.6%	18
Other												
Increase resistance to bearing motion	1	0.1%	0.23	1	0.2%	0.23	0	0.0%	N/A	0	0.0%	N/A
Abductor Rupture	1	0.1%	16	0	0.0%	N/A	1	0.4%	16	0	0.0%	N/A
*Unknown	1	0.1%	31	1	0.2%	31	0	0.0%	N/A	0	0.0%	N/A
Pain	2	0.2%	17	1	0.2%	11	0	0.0%	N/A	0	0.0%	N/A
Total	66	8.0%	18	36	6.7%	19	19	7.0%	22	11	6.9%	29

Note:
* bilateral after 2 years

It should be noted that not all of the 66 revisions in the CONSERVE® Plus Total Resurfacing Hip System All Enrolled Audited cohort were deemed to be device-related. Of the 66 revisions, 57 were deemed device-related and 9 were deemed non-device-related. Two patients were revised for impingement, 1 for abductor rupture, 1 due to acetabular protrusion, and 4 for infection. All 8 of these revisions were deemed to be non-device related. One patient was revised for unknown reasons and was not evaluable by the Data Safety Monitoring Board (DSMB).

Revision rates for the All Enrolled TRANSCEND® Ceramic and All Enrolled TRANSCEND® Metal controls were 29 (5.11%) out of 568 procedures and 20 (6.56%) out of 305 procedures, respectively, at the 24+ Month interval. Revision rates for the Pivotal Efficacy TRANSCEND® Ceramic and Pivotal Efficacy TRANSCEND® Metal controls were 10 (3.85%) out of 260 procedures and 15 (6.02%) out of 249 procedures, respectively, at the 24+ Month interval.

Device Failure Risk Analysis

Methods

Risk Factor Analyses were performed to identify factors associated with increased risk of device failure. These analyses were performed for the All Enrolled Unilateral (Original Shell) cohort (N=680), the Pivotal Unilateral Efficacy cohort (Original Shell) (N=292) and the Bilateral (Original Shell) (N=203) cohort. Data to evaluate potential risk factors were collected as part of a retrieval analysis or during the clinical study.

Retrieval Analysis

At revision, the femoral components were resected with a portion of the femoral neck where possible, and immediately fixed in buffered formalin. If the acetabular components were also removed, these were fixed in formalin as well. The components were inspected, photographed, and then in selected cases (long term, or when unusual wear was expected) measured for wear depth and clearance using a coordinate measuring machine with 2 micron resolution at an independent laboratory. In the early period of the study, femoral components were sectioned into a variable number of sections to allow inspection of the cement/ bone interfaces and access to samples of the bone from various locations for decalcified histological analysis. Later, a more systematic sectioning protocol was followed to facilitate comparison between specimens (i.e., a slice was taken from the anterior and posterior segments equidistant from the middle). After decalcification, paraffin embedding and H & E staining, the sections were inspected. Finally, the general appearance of the tissues was used to determine if the failure was related to avascular necrosis, cement interface loosening or infection using standard histopathological criteria.

Variables Assessed in Risk Factor Analysis

Data for the following variables were collected either as part of a retrieval analysis study or clinical study:

Variables assessed via retrieval analysis:
• Non-osteoarthritis diagnosis
• Avascular Necrosis
• Large (>1cm) and/or multiple femoral cysts
• Poor bone quality such as loss of femoral head bone
• DEXA scan showing severe osteopenia
• Absence of collagen disease
• Femoral neck notching during implantation
• Impacting femoral component beyond surgical technique recommendations
• Failing to suction excess blood or bone debris before femoral component implantation
• Increased number of drilled holes in top of femoral head along with chamfer holes
• Incomplete removal of cystic debris in femoral head
• Removal of anterior osteophyte
• Too much bone removal either on the acetabular or femoral side
• Loss of acetabular press-fit either during initial operation or post-operatively
• Improper distribution of cement
• Leaving the femoral component proud on the femoral head
• Malpositioning of the acetabular component (<30° or >60°)

Variables assessed via clinical data:
• Female vs. male gender
• A non-osteoarthritis diagnosis (AVN, Traumatic Arthritis, Congenital Hip Dysplasia, Rheumatoid Arthritis)
• Pre-surgical Harris Hip Score in the lowest quartile (defined as less than 43.6 points)
• Pre-surgical Harris Hip pain category rated as 'marked pain' or worse
• Any previous treatment on involved hip (i.e., osteotomy, core decompression, hemi-resurfacing, or internal fixation)
• Other joint involvement
• Any bone graft used during procedure
• Presence of femoral cysts (single vs. none and multiple v. none)
• Procedures done within first 60 at a specific site {learning curve effect}
• Small femoral component (≤ 44mm)
• Femoral neck angle (<135) in relation to the femoral shaft
• Femoral component stem angle (<135) in relation to the femoral shaft
• Horizontal acetabular component (< 30 degrees)
• Vertical acetabular component (>60 degrees)

Key Findings

Analysis of the above variables led to the determination of risk factors. For the retrieval analysis, a variable was deemed a risk factor if findings of at least one specimen suggested failure due to that variable. Of the 66 revised implants from the All Enrolled Audited cohort, 37 were available for retrieval analysis. Variables meeting the definition of risk factor from those analyses included:

- diagnosis of traumatic arthritis, congenital hip dysplasia, or avascular necrosis,
- large (>1cm) and/or multiple femoral cysts,
- poor bone quality such as loss of femoral head bone,
- DEXA scan showing severe osteopenia,
- femoral neck notching during implantation,
- impacting femoral component beyond surgical technique recommendations,
- failing to suction excess blood or bone debris before femoral component implantation,
- too few or too many drilled holes in top of femoral head along with chamfer holes,
- incomplete removal of cystic debris in femoral head,
- removal of anterior osteophyte,
- too much bone removal either on the acetabular or femoral side,
- loss of acetabular press-fit either during initial operation or post-operatively,
- improper distribution of cement,
- leaving the femoral component proud on the femoral head, and
- malpositioning of the acetabular component (<30° or >60°).

Risk factors were also determined based on clinical data collected within the study. Table 9 provides a summary of the risk of revision in the All Enrolled Unilateral (Original Shell) cohort, Pivotal Unilateral Efficacy cohort (Original Shell), and Bilateral (Original Shell) cohort.

Table 9: Risk of Revision in All Enrolled Unilateral (Original Shell), Pivotal Unilateral Efficacy Cohort (Original Shell), and Bilateral (Original Shell)
Stratified by All Procedures in Cohort and Only Procedures with At Least 24 Months Follow-up

		All Enrolled Unilateral (Original Shell)	All Enrolled Unilateral (Original Shell) 24+ month follow-up	Pivotal Unilateral Efficacy Cohort[1] (Original Shell)	Pivotal Unilateral Efficacy Cohort (Original Shell) 24+ month follow-up	Bilateral (Original Shell)	Bilateral (Original Shell) 24+ month follow-up
	Revisions	36	36	19	19	11	11
	N	680	540	292	270	203	160
	%	5.3	6.7	6.5	7.0	5.4	6.9
Female gender	Female	7.7% (15/196)	9.0% (15/167)	11.1% (10/90)	11.5% (10/87)	16.0% (8/50)	18.2% (8/44)
	Male	4.3% (21/484)	5.6% (21/373)	4.5% (9/202)	4.9% (9/183)	2.0% (3/153)	2.6% (3/116)
Non osteoarthritis DX	AVN/RA+	8.7% (14/161)	11.1% (14/126)	6.5% (4/62)	7.0% (4/57)	9.1% (4/44)	12.5% (4/32)
	Osteoarthritis	4.2% (22/519)	5.3% (22/414)	6.5% (15/230)	7.0% (15/213)	4.4% (7/159)	5.5% (7/128)
Baseline HHS < 43.6 (1st quartile)[2]	HHS<43.6	4.7% (8/169)	6.1% (8/132)	5.1% (4/78)	5.8% (4/69)	3.3% (2/61)	4.3% (2/47)
	HHS>=43.6	5.4% (27/496)	6.8% (27/400)	7.1% (15/212)	7.5% (15/199)	6.7% (9/135)	8.1% (9/111)
Baseline Pain >=Marked[3]	Marked/Disabled	5.3% (21/393)	6.6% (21/319)	6.1% (11/181)	6.6% (11/167)	3.3% (4/122)	4.3% (4/93)
	Other	5.3% (15/285)	6.8% (15/220)	7.3% (8/110)	7.8% (8/102)	8.8% (7/80)	10.4% (7/67)
Any Previous Treatment	Prev Treatment	6.3% (6/96)	7.5% (6/80)	8.9% (4/45)	9.3% (4/43)	20.0% (2/10)	28.6% (2/7)
	none	5.1% (30/584)	6.5% (30/460)	6.1% (15/247)	6.6% (15/227)	4.7% (9/193)	5.9% (9/153)
Other Joint Involvement	Joint Involved	9.3% (16/172)	12.4% (16/129)	9.3% (7/75)	10.1% (7/69)	5.9% (10/170)	7.6% (10/132)
	none	3.9% (20/508)	4.9% (20/411)	5.5% (12/217)	6.0% (12/201)	3.0% (1/33)	3.6% (1/28)
Any Bone Graft	Bone Graft	4.3% (7/164)	5.4% (7/130)	7.9% (5/63)	8.6% (5/58)	2.9% (1/35)	3.3% (1/30)
	none	5.6% (29/516)	7.1% (29/410)	6.1% (14/229)	6.6% (14/212)	6.0% (10/168)	7.7% (10/130)
Femoral Cysts (Multiple vs not multiple)	>1	4.0% (8/199)	4.7% (8/171)	3.4% (3/89)	3.5% (3/85)	12.0% (6/50)	14.3% (6/42)
	0,1	5.8% (28/481)	7.6% (28/369)	7.9% (16/203)	8.6% (16/185)	3.3% (5/153)	4.2% (5/118)
Femoral Cysts (Any vs none)	Any	6.5% (10/153)	8.3% (10/120)	12.2% (9/74)	12.9% (9/70)	1.8% (1/55)	2.2% (1/45)
	None	4.9% (26/527)	6.2% (26/420)	4.6% (10/218)	5.0% (10/200)	6.8% (10/148)	8.7% (10/115)
1st 60 procedures at a specific site	Within 1st 60	8.0% (28/350)	9.1% (28/308)	7.7% (18/234)	8.2% (18/220)	11.0% (10/91)	12.0% (10/83)
	After 1st 60	2.4% (8/330)	3.4% (8/232)	1.7% (1/58)	2.0% (1/50)	0.9% (1/112)	1.3% (1/77)
Small Femoral Component	< 44	9.0% (18/199)	10.5% (18/171)	12.5% (12/96)	13.2% (12/91)	19.5% (8/41)	22.2% (8/36)
	>=44	3.7% (18/481)	4.9% (18/369)	3.6% (7/196)	3.9% (7/179)	1.9% (3/162)	2.4% (3/124)
Femoral Comp. Neck angle<135°[4,5]	<135°	4.8% (17/354)	5.4% (17/313)	6.3% (12/192)	6.6% (12/181)	5.1% (5/99)	5.7% (5/87)
	>=135°	5.0% (16/318)	7.2% (16/223)	4.2% (4/96)	4.7% (4/86)	5.0% (5/100)	6.9% (5/72)
Stem Neck angle<135°[4,5]	<135°	4.1% (10/246)	4.6% (10/216)	6.1% (7/114)	6.5% (7/108)	4.4% (3/68)	5.1% (3/59)
	>=135°	5.4% (23/426)	7.2% (23/320)	5.2% (9/174)	5.7% (9/159)	5.3% (7/131)	7.0% (7/100)
Too Horizontal Acetabular Component (<30° vs not <30°)[4,6]	<30°	12.5% (5/40)	14.7% (5/34)	13.8% (4/29)	14.3% (4/28)	18.8% (3/16)	21.4% (3/14)
	not <30°	4.4% (28/632)	5.6% (28/502)	4.6% (12/259)	5.0% (12/239)	3.8% (7/184)	4.8% (7/145)
Too Vertical Acetabular Component[4,6]	>60°	4.9% (33/672)	6.2% (33/536)	5.6% (16/288)	6.0% (16/267)	5.0% (10/200)	6.3% (10/159)
	not <60°						

Note:
1. There were no Rheumatoid Arthritis patients included in the Pivotal Unilateral Efficacy Cohort (Original Shell).
2. Regarding Baseline HHS < 43.6 (1st Quartile): 15 evaluations in the All Enrolled Unilateral Cohort (Original Shell), 8 evaluations in the All Enrolled Unilateral Cohort (Original Shell) 24+ Month follow-up, 2 evaluations in the Pivotal Unilateral Efficacy Cohort (Original Shell), 2 evaluations in the Pivotal Unilateral Efficacy Cohort 24+ Month follow-up, 8 evaluations in the Bilateral Cohort (Original Shell) and 2 evaluations in the Bilateral Cohort (Original Shell) 24+ Month follow-up had an incomplete HHS evaluation at Baseline.
3. Regarding Baseline Pain >/= Marked: 2 evaluations in the All Enrolled Unilateral Cohort (Original Shell), 1 evaluation in the All Enrolled Unilateral Cohort (Original Shell) 24+ Month follow-up, 1 evaluation in the Pivotal Unilateral Efficacy Cohort (Original Shell), 1 evaluation in the Pivotal Unilateral Efficacy Cohort 24+ Month follow-up, and 1 evaluation in the Bilateral Cohort (Original Shell) had an incomplete Harris Hip Score Pain assessment at Baseline.
4. Regarding Femoral Component Neck Angle, Stem Neck Angle, Too Horizontal Acetabular Component, and Too Vertical Acetabular Component: 8 evaluations in the All Enrolled Unilateral Cohort (Original Shell), 4 evaluations in the All Enrolled Unilateral Cohort (Original Shell) 24+ Month

follow-up, 4 evaluations in the Pivotal Unilateral Efficacy Cohort (Original Shell), 3 evaluations in the Pivotal Unilateral Efficacy Cohort 24+ Month follow-up did not have baseline post-operative radiographic evaluation performed.
[5.] 4 evaluations in the Bilateral Cohort (Original Shell) did not have Femoral neck or stem angle assessed at the baseline.
[6.] 3 evaluations in the Bilateral Cohort (Original Shell) did not have Acetabular cup inclination assessed at the baseline.

Table 10 summarizes the Cox proportional hazards regression analyses for each variable assessed for the Pivotal Unilateral Efficacy (Original Shell), All Enrolled Unilateral (Original Shell) and Bilateral (Original Shell) cohorts. Variables were analyzed and deemed risk factors if the lower bound of the 95% confidence interval for the hazards ratio was ≥ 1. On the basis of that statistical definition of risk factor, eight variables were deemed risk factors:

- female gender,
- small femoral component (≤ 44mm),
- procedures within the surgeon's first 60 cases,
- diagnosis of avascular necrosis, traumatic arthritis, congenital hip dysplasia, or rheumatoid arthritis,
- any previous treatment to the hip,
- multiple femoral cysts,
- acetabular component position of < 30°, and
- any other joint involvement.

Table 10:
Cox Regression Hazard Ratios and 95% Confidence Intervals for Each Potential Revision Risk Factor Evaluated One-at-a-Time

		Pivotal Unilateral Efficacy Cohort (Original Shell)	All Enrolled Unilateral (Original Shell)	Bilateral (Original Shell)
	Revisions	19	36	11
	N = Overall	292	680	203
	N = Month 24+	270	540	160
	%	7.0%	6.7%	6.9%
Female gender	Hazard	2.24	1.63	6.87
	LB	0.91	0.84	1.82
	UB	5.55	3.17	25.96
Non osteoarthritis Diagnoses	Hazard	0.77	1.98	2.17
	LB	0.24	1.00	0.63
	UB	2.42	3.89	7.45
Any Previous Treatment	Hazard	1.33	1.11	5.57
	LB	0.44	0.46	1.19
	UB	4.04	2.68	26.00
Other Joint Involvement	Hazard	1.79	2.61	2.19
	LB	0.70	1.35	0.28
	UB	4.55	5.05	17.15
Femoral Cysts Multiple vs none	Hazard	0.61	0.65	3.43
	LB	0.16	0.30	1.05
	UB	2.37	1.43	11.26
Procedures done	Hazard	3.68	2.60	7.39

within first 60	LB	0.49	1.17	0.92
at a specific site	UB	27.80	5.77	59.13
Small Femoral	Hazard	3.34	2.26	9.73
Component	LB	1.31	1.17	2.58
	UB	8.50	4.34	36.70
	Hazard	3.04	2.54	6.37
Acetabular Comp.	LB	0.98	0.98	1.59
<30° vs not <30°	UB	9.47	6.61	25.56

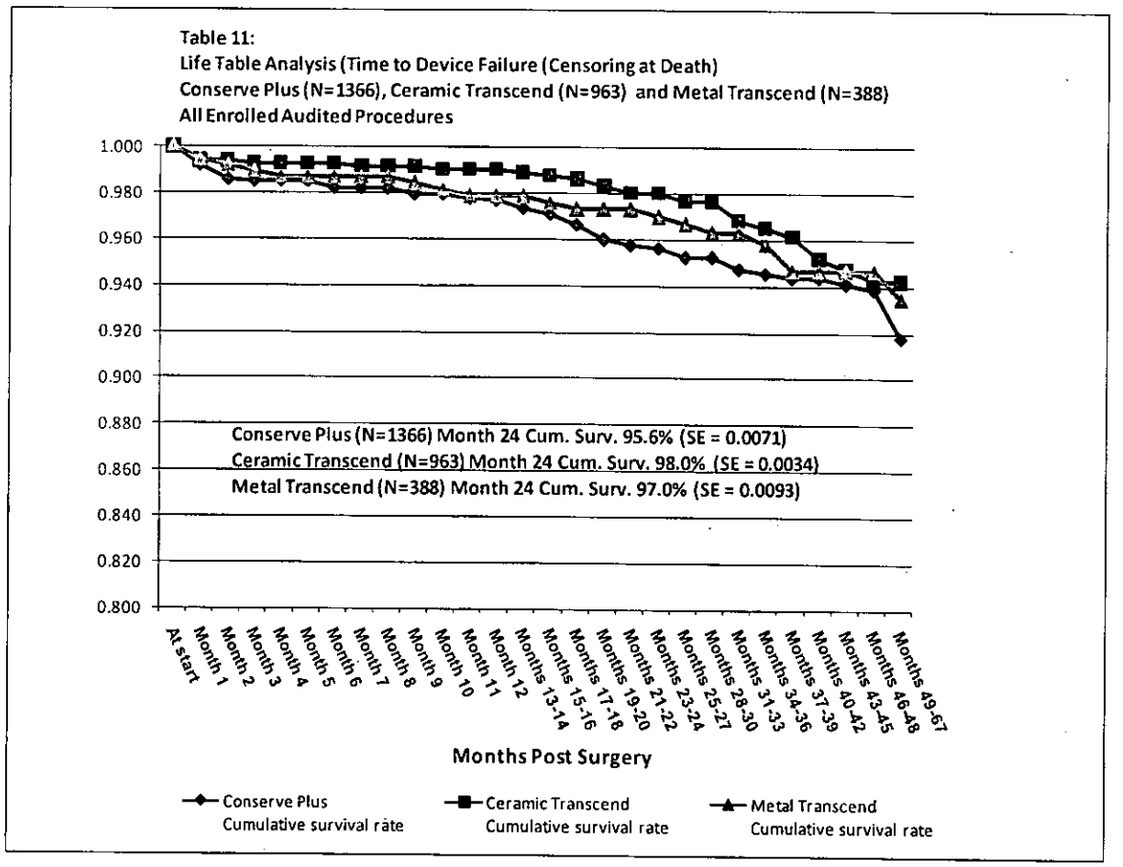
In summary, all risk factors pertain to surgical training and technique and/or patient selection. Therefore, obtaining adequate surgeon training, and consideration of these surgical technique and patient selection risks factors may help decrease the risk of device failure.

Survival Analyses – All Enrolled Audited Cohort
Device survival analyses were performed for the following cohorts:

- CONSERVE® Plus All Enrolled Audited cohort (1366 procedures in 1206 patients) as compared to the Ceramic THR (C1) and Metal THR (C2) Controls [Table 11].
- CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) (N=292 patients) as compared to the Ceramic THR (C1) and Metal THR (C2) Controls [Table 12].

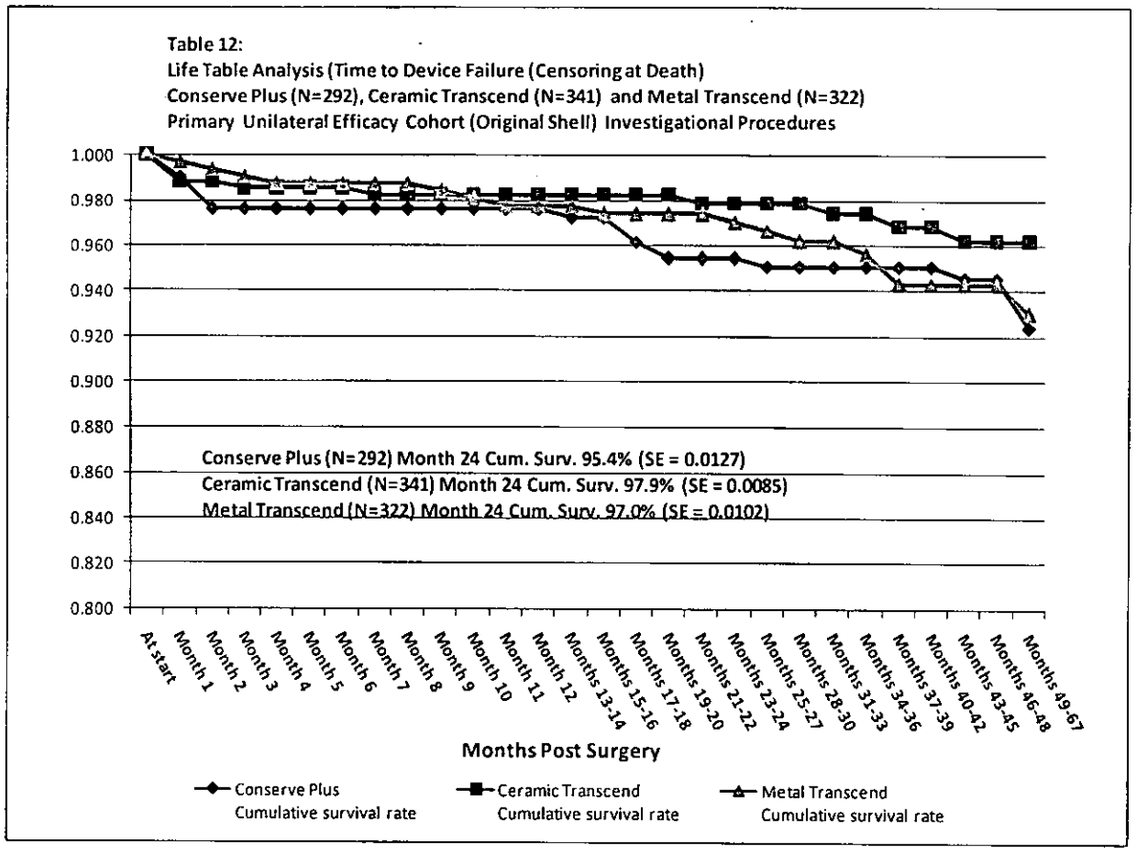
For each cohort listed above, life-tables were tabulated indicating the number of failures and the number of at-risk procedures over time. Since the number of patients at risk (i.e., being followed) diminishes over time, Peto's method[7] was used to determine standard errors for estimates of cumulative survival. Kaplan-Meier survival curves[8] were plotted on the same graph for the three All Enrolled cohorts in order to facilitate graphical comparisons of survivorship over time.

There was a total of 66 procedures requiring revision, replacement, or removal prior to November 20, 2006 among the 1366 All Enrolled Audited CONSERVE® Plus procedures. Of these, 49 procedures required revision on or before the 2-year anniversary date (i.e., within 730 days of the date of surgery). At the same 2-year timepoint, there were 16 of 963 and 11 of 388 procedures requiring revision, replacement, or removal, in the TRANSCEND® Ceramic (C1) and Metal (C2) control patients, respectively. Cumulative 2-year survival rates (Standard Error (SE)) for CONSERVE® Plus, TRANSCEND® Ceramic (C1) , and TRANSCEND® Metal (C2) control patients were 0.956 (SE = 0.0071), 0.980 (SE = 0.0034), and 0.970 (SE = 0.0093), respectively (Table 11). The survival distributions did not significantly differ between CONSERVE® Plus and TRANSCEND® Metal (C2) control at two years (log-rank p=0.30) or based on all available follow-up (log-rank p=0.42). In contrast, survival distributions were significantly lower for the CONSERVE® Plus device as compared to the TRANSCEND® Ceramic (C1) control at two years (log-rank p=0.004) as well as based on all available follow-up (p=0.02).



Survival analyses – Pivotal Unilateral Efficacy Cohort (Original Shell)

There was a total of 19 procedures requiring revision, replacement, or removal prior to November 20, 2006 among the 292 Pivotal Unilateral Efficacy cohort (Original Shell) CONSERVE® Plus procedures. Of these, 13 procedures required revision on or before the 2-year anniversary date (i.e., within 730 days of the date of surgery). At the same 2-year timepoint, there were 7 of 341 and 9 of 322 procedures requiring revision, replacement, or removal, in the TRANSCEND® Ceramic (C1) and TRANSCEND® Metal (C2) control patients, respectively. Cumulative 2-year survival rates (SE) for CONSERVE® Plus, TRANSCEND® Ceramic (C1) , and TRANSCEND® Metal (C2) control patients were 0.955 (0.0127), 0.979 (0.0085), and 0.970 (0.0102), respectively (Table 12). There were no statistically significant differences in survival rates between Groups.



Summary of Adverse Events

CONSERVE® Plus (Group I) device-related and other specific adverse events (complications) were compared to the TRANSCEND® Ceramic (Group C1) and TRANSCEND® Metal (Group C2) control groups for the All Enrolled Audited cohorts.

An independent Data Safety Monitoring Board (DSMB) was convened to assess complications for all three device Groups. The DSMB consisted of independent orthopedic surgeons who were not investigators in the CONSERVE® Plus IDE. The approach taken by the DSMB for evaluation of control group complications was to assess severity and relatedness for only those complications deemed to be hip-related by the study investigators. The approach taken by the DSMB for evaluation of investigational group complications was to assess relatedness for all complications and severity for all device/procedure-related complications. The total pool of complications submitted to the DSMB for review included many unrelated to the device or to the surgery. Among this inclusive pool, the primary safety endpoint was defined to be the occurrence of any complication which the DSMB deemed both severe and at least possibly device-related.

Among the All Enrolled Audited procedures, 67 of 1366 (4.9%) CONSERVE® Plus procedures, 29 of 963 (3.0%) TRANSCEND® Ceramic (C1) controls, and 20 of 388 (5.2%) TRANSCEND® Metal (C2) controls experienced at least one complication assessed by the DSMB as severe and as possibly, probably, or definitely device-related (Table 13). There was a statistically significantly higher complication rate for the CONSERVE® Plus device as compared to the TRANSCEND® Ceramic (C1) control (Fisher's exact test p=0.026). In contrast, there was no statistically significant difference between CONSERVE® Plus and

TRANSCEND® Metal (C2) control (Fisher's exact test p=0.79). For specific hip-related complications that led to these observed differences, please see Table 14.

Table 13:
Comparisons of Summary Complication Rates between All Enrolled Audited Cohort and Control Procedures[1]

	All Enrolled Audited (I) (N=1366)		Ceramic THR Control (C1) (N=963)		Metal THR Control (C2) (N=388)		I vs. C1	I vs. C2
	n	%	n	%	n	%	p-value[9]	p-value[9]
Any complication (per procedure)	986	72.2%	438	45.5%	203	52.3%	<0.0001	<0.0001
Any hip-related complication[2]	691	50.6%	252	26.2%	129	33.2%	<0.0001	<0.0001
Any device-related complication[3]	302	22.1%	84	8.7%	24	6.2%	<0.0001	<0.0001
Any DSMB device-related complication[4]	531	38.9%	139	14.4%	99	25.5%	<0.0001	<0.0001
Any DSMB procedure-related complication[5]	735	53.8%	203	21.1%	97	25.0%	<0.0001	<0.0001
Any DSMB severe complication[6]	233	17.1%	30	3.1%	20	5.2%	<0.0001	<0.0001
Any DSMB device-related severe complication[7]	**67**	**4.9%**	**29**	**3.0%**	**20**	**5.2%**	**0.026**	**0.793**
Any DSMB procedure-related severe complication[8]	103	7.5%	30	3.1%	20	5.2%	<0.0001	0.115
Deaths	7	0.5%	11	1.1%	3	0.8%	0.097	0.468

Notes:
[1] All procedures meeting inclusion/exclusion criteria with a date of surgery on or before the date of database closure are included in the All Enrolled Procedures Cohorts.
[2] Hip-related defined as all local hip complications.
[3] Includes complications possibly, probably, or definitely associated with study device as assessed by the investigator.
[4] DSMB independent review that complication was possibly, probably, or definitely associated with study device.
[5] DSMB independent review that complication was possibly, probably, or definitely associated with the implant procedure.
[6] DSMB independent review that complication was severe or life threatening.
[7] DSMB review that complication was possibly, probably, or definitely associated with the study device and was severe or life-threatening.
[8] DSMB review that complication was possibly, probably, or definitely associated with the procedure and was severe or life-threatening.
[9] P-value from pairwise Fisher's Exact test.

Of the 67 procedures reported by the DSMB as severe device-related complications, 57 resulted in device revisions and 10 did not. The 10 procedures that were reported as severe device related but did not lead to revision are as follows:

- 2 with systemic complications
- 2 with nerve problems
- 2 with pain in the operative hip
- 2 with other complications in the operative hip (1 loss of motion and 1 radiation treatment for heterotopic ossification)
- 2 with infection

The 57 procedures that resulted in revision are identified in Table 8.

There were 7 deaths reported in patients who received the CONSERVE® Plus device. The causes of death are as follows:

- 1 died from a massive cardiac event while bike riding

- 1 died from a pulmonary embolism that was non-device or procedure-related
- 1 died from a cardiac aneurysm
- 1 died from a possible heart attack
- 1 died from lung cancer
- 1 died from recurrent non-small cell lung cancer
- 1 died from a drug overdose
- 1 died from unknown causes

None of the deaths reported were deemed to be device-related.

Hip-related adverse events

Tables 14-17 provide a breakdown of the overall rates of hip-related complications and hip-related complications by time of occurrence for the All Enrolled Audited cohort and Pivotal Unilateral Efficacy cohort (Original Shell) and corresponding cohorts of the control groups. Hip-related complications were defined as all local hip complications related to the operative hip. DSMB hip-related complications were defined as complications that were possibly, probably, or definitely associated with the operative hip. DSMB hip-related severe complications were defined as complications that were possibly, probably, or definitely associated with the operative hip and were severe or life threatening. The listing of complications includes events related to both the hip and the device. This was done to capture all events associated with the operative hip.

The following hip-related AEs were found to be statistically significantly higher for the CONSERVE® Plus All Enrolled Audited cohort when compared to the control group(s).

- 145 procedures with heterotopic ossification when compared to both control groups (p=<0.001); 2/145 (1.4%) were deemed severe.
- 27 procedures with hematoma when compared to the TRANSCEND® Ceramic (C1) control (p=0.001); 0/27 (0.0%) were deemed severe.
- 25 procedures with infection: shallow when compared to the TRANSCEND® Ceramic (C1) control (p=0.005); 0/25 (0.0%) were deemed severe.
- 25 procedures with loosening of the femoral or acetabular component when compared to the TRANSCEND® metal (C2) control (p=0.017); 22/25 (88.0%) were deemed severe.
- 27 procedures with nerve problems when compared to both control groups (p=0.014 for the TRANSCEND® Ceramic (C1) control and p=0.002 for the TRANSCEND® metal (C2) control); 0/27 (0.0%) were deemed severe.
- 367 procedures with pain when compared to both control groups (p=<0.001); 9/367 (2.5%) were deemed severe. Also, reported within this group were 4/367 (1.09%) cases in which clicking, popping, squeaking or grinding was reported with the pain, none were deemed severe.
- 42 procedures with wound problems when compared to both control groups (p=<0.001); 0/42 (0.0%) were deemed severe.
- 201 procedures with other local hip complications when compared to both control groups (p=<0.001); 12/201 (6.0%) were deemed severe. Also, reported within this group were 20/201 (9.95%) cases in which clicking, popping, squeaking or grinding was reported, none were deemed severe.
- 26 procedures with trochanteric bursitis when compared to the TRANSCEND® metal (C2) control (p=0.012); 0/26 (0.0%) were deemed severe.

Table 14:
Comparisons of Percentages with Specific Complications between All Enrolled Audited Cohort and Ceramic THR and Metal THR Control Procedures[1]

	All Enrolled Audited (I) (N=1366)		Ceramic THR Control (C1) (N=963)		Metal THR Control (C2) (N=388)		I vs. C1	I vs. C2
	n	%	n	%	n	%	p-value[2]	p-value[2]
Ankylosis	0	0.0%	0	0.0%	3	0.8%	.	0.011
Breakage/fracture of component	7	0.5%	7	0.7%	1	0.3%	0.590	1.000
Dislocation (initial) of component	15	1.1%	16	1.7%	10	2.6%	0.273	0.048
Dislocation (recurrent) of component	4	0.3%	5	0.5%	1	0.3%	0.502	1.000
Fracture of bone	30	2.2%	20	2.1%	6	1.5%	0.886	0.544
Heterotropic ossification	145	10.6%	55	5.7%	18	4.6%	<0.001	<0.001
Hematoma	27	2.0%	4	0.4%	6	1.5%	0.001	0.677
Hemarthrosis	0	0.0%	0	0.0%	3	0.8%	.	0.011
Infection: deep, early<1yr	8	0.6%	7	0.7%	2	0.5%	0.794	1.000
Infection: deep, late>1yr	6	0.4%	2	0.2%	1	0.3%	0.482	1.000
Infection: Shallow	25	1.8%	5	0.5%	8	2.1%	0.005	0.832
Loosening of component	25	1.8%	9	0.9%	1	0.3%	0.081	0.017
Migration of component	7	0.5%	2	0.2%	1	0.3%	0.321	1.000
Nerve problem	27	2.0%	7	0.7%	20	5.2%	0.014	0.002
Pain	367	26.9%	88	9.1%	58	14.9%	<0.001	<0.001
Pain with clicking, popping, squeaking or grinding	4	0.3%	5	0.5%	2	0.5%	0.502	0.619
Perforation	1	0.1%	2	0.2%	0	0.0%	0.573	1.000
Reflex sympathethic dystrophy	0	0.0%	0	0.0%	2	0.5%	.	0.049
Wear of component	0	0.0%	1	0.1%	0	0.0%	0.414	.
Subsidence of component	2	0.1%	4	0.4%	4	1.0%	0.239	0.024
Wound problems	42	3.1%	9	0.9%	0	0.0%	<0.001	<0.001
Other local hip complication	201	14.7%	56	5.8%	26	6.7%	<0.001	<0.001
Clicking, popping, squeaking or grinding	20	1.5%	19	2.0%	2	0.5%	0.413	0.196
Trochanteric bursitis	26	1.9%	35	3.6%	6	1.5%	0.012	0.830
Subluxation	2	0.1%	0	0.0%	1	0.3%	0.515	0.528
Osteolysis	3	0.2%	0	0.0%	1	0.3%	0.272	1.000

Notes:
[1] All procedures meeting inclusion/exclusion criteria with a date of surgery on or before the date of database closure are included in the All Enrolled Audited Cohorts.
[2] Fisher's exact test.

Table 15:
Specific Complications by Time of Occurrence per Procedure
All Enrolled Audited Cohort {N=1366} (I), Ceramic THR Control {N=963} (C1), and Metal THR Control {N=388} (C2) Procedures

	Pre Discharge			Post Discharge to Month 6			Month 6 to Month 12			Month 12 to Month 24			Month 24 +			Total		
	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2
Ankylosis									2			1				0	0	3
Breakage/fracture of component		5	1	1						3	1		3	1		7	7	1
Dislocation (initial) of component	3	2	2	10	11	5		1			1	2	2	1	1	15	16	10
Dislocation (recurrent) of component		1		4	4								1		1	4	5	1
Fracture of bone		15	3	16	3		5			5	1		4	1	3	30	20	6
Heterotropic ossification	13			68	17	2	29	12	3	25	15	9	12	11	4	145	55	18
Hematoma			2	23	3	3	1		1	1			2	1		27	4	6
Hemarthrosis						2						1				0	0	3
Infection: deep, early<1yr				6	4	2	2			1	1			2		8	7	2
Infection: deep, late>1yr				1						4	1	1	1	1		6	2	1
Infection, shallow				24	3	3	1	2	1						4	25	5	8
Loosening of component	1			6			13	3		5	3		10	3	1	25	9	1
Migration of component	2				1					4			1	1	1	7	2	1
Nerve problem	14	2		11	2	2	1	1	5	1		6		2	7	27	7	20
Pain	11	3		130	35	17	76	21	12	68	10	9	82	19	20	367	88	58
Pain with clicking, popping, squeaking or grinding				1						1	1		2	4	2	4	5	2
Perforation	1	2														1	2	0
Reflex sympathetic dystrophy													1		2	0	0	2
Wear of component								1								0	1	0
Subsidence of component		1	2		2	1				1	1	1	1			2	4	4
Wound problems	7			32	8		1			1	1		1			42	9	0
Other local hip complication	19	4	1	80	14	7	42	12	3	29	13	12	31	13	3	201	56	26
Clicking, popping, squeaking or grinding				2	2		7	4		5	2		6	11	2	20	19	2
Trochanteric bursitis				10	9	1	6	3	1	5	16		5	7	4	26	35	6
Subluxation				2											1	2	0	1
Osteolysis				1		1	1						1			3	0	1

Table 16:
Comparisons of Percentages with Specific Complications between Pivotal Unilateral Efficacy Cohort (Original Shell) (I) versus Ceramic (C1) and Metal (C2) THR Unilateral Efficacy Cohorts[1]

	Pivotal Unilateral Efficacy Cohort (Original Shell) (I) (N=292)		Ceramic THR Control (C1) (N=341)		Metal THR Control (C2) (N=322)		I vs. C1	I vs. C2
	n	%	n	%	n	%	p-value[2]	p-value[2]
Ankylosis	0	0.0%	0	0.0%	3	0.9%	.	0.251
Breakage/fracture of component	3	1.0%	4	1.2%	1	0.3%	1.000	0.351
Dislocation (initial) of component	3	1.0%	4	1.2%	9	2.8%	1.000	0.148
Dislocation (recurrent) of component	1	0.3%	1	0.3%	1	0.3%	1.000	1.000
Fracture of bone	11	3.8%	7	2.1%	6	1.9%	0.234	0.218
Heterotropic ossification	44	15.1%	23	6.7%	15	4.7%	0.0007	<0.001
Hematoma	3	1.0%	1	0.3%	6	1.9%	0.340	0.509
Hemarthrosis	0	0.0%	0	0.0%	2	0.6%	.	0.500
Infection: deep, early<1yr	1	0.3%	1	0.3%	2	0.6%	1.000	1.000
Infection: deep, late>1yr	1	0.3%	1	0.3%	1	0.3%	1.000	1.000
Infection: Shallow	4	1.4%	2	0.6%	7	2.2%	0.422	0.551
Loosening of component	6	2.1%	1	0.3%	1	0.3%	0.053	0.058
Migration of component	0	0.0%	2	0.6%	1	0.3%	0.502	1.000
Nerve problem	3	1.0%	3	0.9%	14	4.3%	1.000	0.013
Pain	87	29.8%	39	11.4%	50	15.5%	<0.001	<0.001
Pain with clicking, popping, squeaking or grinding	2	0.7%	1	0.3%	2	0.6%	0.598	1.000
Perforation	0	0.0%	0	0.0%	0	0.0%	.	.
Reflex sympathethic dystrophy	0	0.0%	0	0.0%	2	0.6%	.	0.500
Wear of component	0	0.0%	1	0.3%	0	0.0%	1.000	.
Subsidence of component	1	0.3%	3	0.9%	4	1.2%	0.628	0.376
Wound problems	6	2.1%	4	1.2%	0	0.0%	0.525	0.011
Other local hip complication	55	18.8%	23	6.7%	23	7.1%	<0.001	<0.001
Clicking, popping, squeaking or grinding	6	2.1%	10	1.0%	2	0.6%	0.614	0.159
Trochanteric bursitis	10	3.4%	18	5.3%	6	1.9%	0.333	0.311
Subluxation	1	0.3%	0	0.0%	0	0.0%	0.461	0.476
Osteolysis	2	0.7%	0	0.0%	1	0.3%	0.212	0.607

Notes:
[1] Pivotal unilateral efficacy cohort, ceramic THR primary unilateral efficacy cohort, and all metal THR unilateral procedures.
[2] Fisher's exact test.

Table 17:
Specific Complications by Time of Occurrence per Procedure
Pivotal Unilateral Efficacy Cohort (Original Shell) {N=292} (I), Ceramic THR Control {N=341} (C1), and Metal THR Control {N=322} (C2) Procedures

	Pre Discharge			Post Discharge to Month 6			Month 6 to Month 12			Month 12 to Month 24			Month 24 +			Total		
	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2	I	C1	C2
Ankylosis									2						1	0	0	3
Breakage/fracture of component		4	1							2			1			3	4	1
Dislocation (initial) of component	1	2	1	1	2	5				1		1			2	3	4	9
Dislocation (recurrent) of component	1	1		1								1				1	1	1
Fracture of bone		6	3	6			1			1	1	3	3			11	7	6
Heterotropic ossification				20	6	1	12	6	3	5	5	4	7	6	7	44	23	15
Hematoma			2	3		3			1		1					3	1	6
Hemarthrosis				1		2										0	0	2
Infection: deep, early<1yr				1	1	2										1	1	2
Infection: deep, late>1yr							1			1	1				1	1	1	1
Infection, shallow				4	1	2		1	1			4				4	2	7
Loosening of component				1						3		1	2	1		6	1	1
Migration of component					1						1	1				0	2	1
Nerve problem	2	2		1	1	1			3			5			5	3	3	14
Pain	5	1		22	13	15	14	11	10	35	8	18	11	6	7	87	39	50
Pain with clicking, popping, squeaking or grinding				1							1		1		2	2	1	2
Perforation																0	0	0
Reflex sympathetic dystrophy												2				0	0	2
Wear of component								1								0	1	0
Subsidence of component		1	2		1	1				1				1	1	1	3	4
Wound problems				6	4											6	4	0
Other local hip complication	4		1	16	5	7	13	4	3	11	10	3	11	4	9	55	23	23
Clicking, popping, squeaking or grinding				2	1			1		2			2	8	2	6	10	2
Trochanteric bursitis				3	3	1	2	1	1	4	5	4	1	9		10	18	6
Subluxation				1												1	0	0
Osteolysis				1		1	1									2	0	1

Device-related adverse events

Device-related adverse events were defined as post-operative complications concerning the device related to the design, and/or material composition of the implant and implantation technique. DSMB device-related complications were defined as complications that were possibly, probably, or definitely associated with the study device. DSMB device-related severe complications were defined as complications that were possibly,

probably, or definitely associated with the study device and were severe or life threatening. Table 18 provides a breakdown of the rates of severe device-related complications for the All Enrolled Audited cohort and the corresponding cohorts of the control groups.

It should be noted that some device-related adverse events reported in Table 18 did not result in revision during the course of the clinical study; therefore, do not appear in Table 8. In addition, some of the reasons for device revision were non-device related. Of the 28 fractures of bone reported in Table 8, 26 were deemed to be device-related by the DSMB. The 2 remaining fractures of bone were not deemed device-related because the fractures were the result of trauma. Twenty-two (22) loosenings of component were reported in Table 18. All of these components were revised but in Table 8 the reasons for revision were reported as follows: 17 revised due to loosening of either the acetabular (10) or femoral component (7); one revised due to acetabular component loosening with femoral neck fracture; three loosenings were revised due to infection; and, 1 patient had a second surgery to reposition a loosened acetabular cup 2 days after the initial procedure.

As shown in Table 18, one procedure had recurrent dislocation. To date, this device has not been revised and, therefore, would not appear in Table 8. Table 8 also reports 8 procedures being revised due to infection. One procedure presented with deep, late (> 1 year) infection that was deemed by the DSMB as device-related, with the remaining 7 being deemed not device-related.

Table 18 reports 5 "breakage/fracture of component" serious device-related complications. For all 5 reports, the femoral stem broke secondary to femoral neck fracture. It should be noted that there were 7 total "breakage /fracture of component" reported on Table 14, 2 of which were not deemed device- related due to trauma. Also, the 11 reported severe device-related "Other local complications" include the following:

- 1 episode of device clunking with sore back
- 1 surgery to remove scar tissue with the device remaining implanted
- 1 case of pseudocapsule release and release of flexors and abductors due to no motion at hip
- 1 patient underwent radiation therapy following removal of heterotopic ossification
- 1 patient had severe stiffness that prevented patient from returning to work
- 1 patient had deformation of the femoral component (stem bent secondary to femoral neck fracture)
- 1 patient had pain secondary to impingement
- 1 patient reported increased resistance hip motion
- 1 patient presented with protrusion of the acetabular cup through the acetabulum
- 1 patient heard a pop when bending over
- 1 patient reported revision, but refused to give information on the cause

Table 18:
Pairwise Comparisons Between All Enrolled Audited Cohort and Control Procedures[1]
Specific DSMB Assessed Severe Device-Related Complication Rates Per Procedure

	All Enrolled Audited (I) (N=1366)		Ceramic THR Control (C1) (N=963)		Metal THR Control (C2) (N=388)		I vs. C1	I vs. C2
	n	%	n	%	n	%	p-value[2]	p-value[2]
Ankylosis	0	0.0%	0	0.0%	3	0.8%	.	0.011
Breakage/fracture of component	5	0.4%	3	0.3%	0	0.0%	1.000	0.593
Dislocation (initial) of component	0	0.0%	1	0.1%	2	0.5%	0.413	0.049
Dislocation (recurrent) of component	1	0.1%	2	0.2%	0	0.0%	0.573	1.000
Fracture of bone	26	1.9%	1	0.1%	1	0.3%	<0.0001	0.017
Heterotropic ossification	2	0.1%	1	0.1%	1	0.3%	1.000	0.528
Hematoma	0	0.0%	0	0.0%	0	0.0%	.	.
Hemarthrosis	0	0.0%	0	0.0%	0	0.0%	.	.
Infection: deep, early<1yr	0	0.0%	0	0.0%	0	0.0%	.	.
Infection: deep, late>1yr	1	0.1%	0	0.0%	0	0.0%	1.000	1.000
Infection: Shallow	0	0.0%	0	0.0%	6	1.5%	.	<0.001
Loosening of component	22	1.6%	8	0.8%	1	0.3%	0.134	0.041
Migration of component	4	0.3%	1	0.1%	0	0.0%	0.655	0.582
Nerve problem	0	0.0%	0	0.0%	2	0.5%	.	0.049
Pain	8	0.6%	3	0.3%	1	0.3%	0.541	0.693
Perforation	1	0.1%	0	0.0%	0	0.0%	1.000	1.000
Reflex sympathethic dystrophy	0	0.0%	0	0.0%	0	0.0%	.	.
Wear of component	0	0.0%	1	0.1%	0	0.0%	0.413	.
Subsidence of component	1	0.1%	2	0.2%	0	0.0%	0.573	1.000
Wound problems	0	0.0%	0	0.0%	0	0.0%	.	.
Other local hip complication	11	0.8%	0	0.0%	0	0.0%	0.004	0.136
Trochanteric bursitis	0	0.0%	0	0.0%	0	0.0%	.	.
Subluxation	0	0.0%	0	0.0%	0	0.0%	.	.
Osteolysis	1	0.1%	0	0.0%	0	0.0%	1.000	1.000

Notes:
[1] All procedures meeting inclusion/exclusion criteria with a date of surgery on or before the date of database closure are included in the All Enrolled Audited Cohort.
[2] Fishers Exact test.

Systemic events

Systemic adverse events were those reported events that did not relate directly to the operation or the operative site/device.

Table 19 provides a summary of the systemic complications for the CONSERVE® Plus All Enrolled Audited (Group I) procedures and the corresponding cohorts of the TRANSCEND® Ceramic (Group C1) and TRANSCEND® Metal (Group C2) control groups. Although statistically significant differences were identified between groups for certain systemic complications, none were device-related.

Table 19:
Comparisons of Percentages with Specific Complications between All Enrolled Audited Cohort and Control Procedures[1]

	All Enrolled Audited (I) (N=1366)		Ceramic THR Control (C1) (N=963)		Metal THR Control (C2) (N=388)		I vs. C1	I vs. C2
	n	%	n	%	n	%	p-value[2]	p-value[2]
Systemic								
Allergic reactions	19	1.6%	4	0.5%	1	0.3%	0.019	0.061
Disseminated intravascular coagulation	0	0.0%	1	0.1%	2	0.6%	0.412	0.052
Fat embolism	1	0.1%	0	0.0%	3	0.8%	1.000	0.039
Gastrointestinal	36	3.0%	14	1.7%	8	2.2%	0.059	0.585
Genitourinary disorders	45	3.7%	15	1.8%	1	0.3%	0.011	<0.001
Metabolic disorders	4	0.3%	0	0.0%	7	2.0%	0.148	0.004
Myocardial infarction	2	0.2%	5	0.6%	5	1.4%	0.132	0.008
Stroke	1	0.1%	1	0.1%	62	17.4%	1.000	<0.0001
Other cardiovascular	36	3.0%	15	1.8%	4	1.1%	0.112	0.055
Pulmonary embolism	5	0.4%	4	0.5%	1	0.3%	1.000	1.000
Other respiratory	16	1.3%	10	1.2%	7	2.0%	0.843	0.451
Septicemia	1	0.1%	1	0.1%	3	0.8%	1.000	0.039
Thrombosis	18	1.5%	6	0.7%	3	0.8%	0.143	0.441
Other systemic complication	145	12.0%	88	10.4%	8	2.2%	0.289	<0.0001

Notes:
[1] All procedures meeting inclusion/exclusion criteria with a date of surgery on or before the date of database closure are included in the All Enrolled Audited Cohorts.
[2] Fisher's exact test.

Systemic complications that demonstrated a statistical difference were seen in the following categories: allergic reactions, gastrointestinal disorders, genitourinary disorders, other cardiovascular disorders and other systemic complications. These are general categories used for analytical purposes. The actual events associated with these general categories are as follows:

- 19 allergic reactions (i.e., rash, dermatitis); None were reported as severe.
- 36 gastrointestinal (i.e., nausea, vomiting, rectal bleeding, diarrhea, abdominal pain, constipation); None were reported as severe.
- 45 genitourinary disorders (i.e., urinary tract infection, urinary retention, kidney stones, prostate cancer, benign prostate hypertrophy); None were reported as severe.
- 36 cardiovascular events (e.g., chest pain, tachycardia, atrial fibrillation, abnormal EKG, coronary artery disease, cardiac aneurysm resulting in death, 2 heart attacks resulting in death); 3/36 (8.3%) were reported as severe.
- 145 Other systemic complications (e.g.,. anemia, swelling in extremities, fever, edema, headache, metastatic lung cancer resulting in death, and Cause of Death unknown); 2/145 (1.4%) were reported as severe.

Metal Ions

While concerns exist with regard to the local and systemic effects of metal ions, in the vast majority of patients there is no direct evidence linking metal-on-metal arthroplasty with long-term medical problems. A study performed on 25 patients with the CONSERVE® Plus Total Resurfacing Hip System was reported by Skipor, *et al.*, in, "Serum and urine metal levels in patients with metal-on-metal surface arthroplasty," *J Mat Sci Mat Med* 13 (2002), p.1227-34.[9] Head sizes for these patients ranged from 38 to 52mm. Serum cobalt and chromium and urine chromium analysis revealed levels that do not differ widely from metal-on-metal values reported in the literature, although they are higher than other bearings. Mean serum cobalt and chromium at 12 months were 1.07 (+/- 0.26) and 1.80 (+/- 0.45) parts per billion (ppb), respectively. Mean urine chromium at 12 months was 2.21 (+/- 0.83) ppb. In summary, while ions will be higher in patients who receive metal-on-metal hip implants versus patients who receive other bearing surfaces (i.e., metal-on-polyethylene, ceramic-on-ceramic), in the vast majority of patients there has been no direct evidence demonstrating that elevated levels adversely effect health.

The Oxford research group presented their findings related to 115 cases in which 6 patients (5 female, 1 male) implanted with 9 hips (3 bilateral, 3 unilateral) presented with 9 pseudotumors and higher median serum cobalt and serum chromium ion levels as compared to those cases without pseudotumors. Moreover, two of these 9 pseudotumors exhibited signs of lymphocyte infiltration indicative of delayed hypersensitivity reaction (ALVAL). This led the authors to conclude that "an asymptomatic pseudotumour in patients with metal-on-metal hip resurfacing is associated with elevated serum cobalt and chromium ion levels, suggesting that abnormal wear may be the cause of pseudotumour. The precise mechanism is unclear and may be due to metal hypersensitivity reaction or toxic effects. "Metal Ion Levels In Asymptomatic Pseudotumours Associated With Metal-on-metal Hip Resurfacings." Kwon, et. al. Paper No. 44, *55th Annual Meeting of the Orthopaedic Research Society, Las Vegas, 2009.*[10]

Appropriate information related to this matter has been included within the labeling.

2. <u>Effectiveness Results</u>

Effectiveness was evaluated primarily by the Composite Clinical Success (CCS) definition. Harris Hip Score, radiographic outcome, and Health Related Quality of Life (SF-12) Scores were also evaluated as a measure of effectiveness.

Harris Hip Score

As seen in Table 20, the mean Month 24+ Harris Hip Total score was 94.4 in the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell). This compares to 94.1 and 92.7 for patients in the TRANSCEND® Ceramic and Metal THR Unilateral Control cohorts, respectively.

Mean 24+ Harris Hip function score was 45.1, 44.4 and 43.4, for CONSERVE® Plus Pivotal Unilateral Efficacy (Original Shell), TRANSCEND® Ceramic, and TRANSCEND® Metal Unilateral control cohorts, respectively.

Mean 24+ Harris Hip Range of Motion (ROM) score was 4.82, 4.88, and 4.81 for the CONSERVE® Plus Pivotal Unilateral Efficacy (Original Shell), TRANSCEND® Ceramic, and TRANSCEND® Metal Unilateral control cohorts, respectively.

Table 20:
Mean Harris Hip Total, Function, and ROM Scores Over Time
Pivotal Unilateral Efficacy Cohort (Original Shell) (I) vs. Ceramic THR (C1) and Metal THR Controls (C2)

	Pivotal Unilateral Efficacy Cohort (I) Harris Hip Total Score[1]					Ceramic Transcend Control (C1) Harris Hip Total Score[1]					Metal Transcend Control (C2) Harris Hip Total Score[1]					T-Test	
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	I vs. C1 p-value [2]	I vs. C2 p-value [2]
Pre-0p	290	49.4	11.7	7.3	77.9	337	45.2	12.8	12.9	89.0	316	47.6	14.2	4.5	89.7	<0.001	0.086
Month 6	204	91.4	9.7	49.0	100.0	291	88.3	13.0	37.7	100.0	257	88.4	13.9	13.6	100.0	0.002	0.006
Month 12	239	93.4	9.7	38.8	100.0	255	92.3	13.0	23.9	100.0	223	91.4	12.0	26.7	100.0	0.272	0.053
Month 24	226	94.9	7.7	59.0	100.0	207	94.4	10.0	33.7	100.0	207	93.1	10.0	38.0	100.0	0.595	0.043
Month 24+	264	94.4	8.5	49.8	100.0	278	94.1	10.8	33.7	100.0	267	92.7	10.7	38.0	100.0	0.727	0.041
	Pivotal Unilateral Efficacy Cohort (I) Harris Hip Function Score					**Ceramic Transcend Control (C1) Harris Hip Function Score**					**Metal Transcend Control (C2) Harris Hip Function Score**						
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	I vs. C1 p-value [2]	I vs. C2 p-value [2]
Pre-0p	291	27.6	8.0	0.0	44.0	337	25.2	8.3	4.0	45.0	316	25.4	8,6	0.0	42.0	<0.001	0.001
Month 6	205	43.0	5.5	5.0	47.0	291	40.2	7.7	7.0	47.0	257	40.1	8.2	5.0	47.0	<0.001	<0.001
Month 12	239	44.6	4.6	14.0	47.0	255	43.4	6.4	5.0	47.0	223	42.6	6.0	8.0	47.0	0.013	<0.001
Month 24	226	45.3	3.4	20.0	47.0	207	44.5	5.3	15.0	47.0	207	43.3	5.1	19.0	47.0	0.070	<0.001
Month 24+	264	45.1	3.5	20.0	47.0	278	44.4	5.4	15.0	47.0	267	43.4	5.1	19.0	47.0	0.076	<0.001
	Pivotal Unilateral Efficacy Cohort (I) Harris Hip ROM Score1					**Ceramic Transcend Control (C1) Harris Hip ROM Score1**					**Metal Transcend Control (C2) Harris Hip ROM Score1**						
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	I vs. C1 p-value [2]	I vs. C2 p-value [2]
Pre-0p	291	4.47	0.61	0.00	5.00	338	4.09	0.97	0.00	5.00	316	4.30	0.60	0.00	5.00	<0.001	<0.001
Month 6	207	4.79	0.77	0.00	5.00	291	4.77	0.33	1.08	5.00	258	4.80	0.36	0.00	5.00	0.824	0.855
Month 12	241	4.89	0.36	0.00	5.00	255	4.82	0.36	0.00	5.00	226	4.85	0.14	4.10	5.00	0.018	0.068
Month 24	229	4.81	0.75	0.00	5.00	207	4.88	0.15	4.23	5.00	207	4.84	0.37	0.00	5.00	0.178	0.658
Month 24+	265	4.82	0.76	0.00	5.00	278	4.88	0.15	4.23	5.00	267	4.81	0.54	0.00	5.00	0.171	0.854

Notes: [1] Post-op Harris Hip Total and ROM scores include procedures with zeros imputed for missing HHS ROM and deformity.
[2] T-Test (Pooled standard error for equal variance and Satterthwaite standard error for unequal variance).

There were 11 hips in the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) that had a Harris Hip Total score <70 at 24+ Months. Of these, 1 hip was painful due to a loose acetabular cup, 3 had sciatica, 1 had cardiovascular complications unrelated to the hip, 1 had hip and knee pain, and 1 had degenerative spondylolisthesis. For 4 of the 11, no reason for the "poor" rating was ascertained.

No statistical differences were seen in the Month 24 and Month 24+ postoperative range of motion values when compared to both control cohorts.

Radiographic outcomes

Radiographic outcomes for the Pivotal Unilateral Efficacy cohort (Original Shell) were summarized based on independent radiographic evaluations as well as investigator evaluation (Tables 21 and 22, respectively). In both cases, the Month 24 cumulative radiolucency summary was computed by categorizing the most severe radiolucencies across zones and time intervals. A cumulative radiolucency was defined as the largest radiolucency identified over time up until and including the Month 24 timepoint.

There were 275 out of 292 Pivotal Study Unilateral (Original Shell) cohort patients with at least one independent radiographic evaluation. In 31 of 275 patients (11.3%), cumulative radiolucencies greater than 2 mm were identified; however, there were no revisions or removals reported within this group. In 26 of 275 (9.5%) cases, cumulative radiolucencies >1 to 2 mm were reported. There was one failure identified in this group due to impingement and not as a result of loosening or migration.

There were 288 out of 292 Pivotal Study Unilateral Patients with at least one investigator-based follow-up radiograph. In 6 of 288 patients (2.1%), cumulative radiolucencies greater than 2 mm were identified. There were no revisions or removals reported within this group. In 11 of 288 (3.8%) patients, radiolucencies >1 to 2mm were reported. There was one failure identified in this group due to impingement and not as a result of loosening or migration. Note: This is the same patient who was reviewed during the independent radiographic assessment.

There were no cases of migration of the cup reported by the independent radiographic reviewer or investigator for the Pivotal Study Unilateral (Original Shell) cohort patients.

In terms of the composite clinical success (CCS) radiographic endpoint, a patient was defined as a success at the Month 24+ follow-up timepoint if there was an absence of complete radiolucency in all four radiographic views. Complete radiolucency in a view was defined to be present if there was any radiolucency present in all zones comprising that view. There was one case of complete radiolucency as identified by the investigator at Month 24 in the Pivotal Study Unilateral (Original Shell) cohort. This patient went on to be revised for acetabular cup loosening.

In addition to the CCS radiographic findings, it was noted that in the Pivotal Study Unilateral (Original Shell) cohort there was 1 case revised due to femoral loosening (Table 8), in which no radiolucencies were identified by independent or investigator radiographic review. There were 3 cases revised due to acetabular loosening (Table 8) in which no radiolucencies were identified by independent radiographic review. As noted in the CCS radiographic findings above, one of these three cases reported complete radiolucency as identified by the investigator at Month 24. This case had radiolucencies (0 to 1mm) identified in all 3 Charnley zones.

Table 21:
Overall Interval Specific and Cumulative Summary of Any Finding of Acetabular or Femoral Radiolucency
Pivotal Study Unilateral Efficacy Cohort (Original Shell) {Independent radiography}

Interval	N	None	>0-1	>1-2	>2	Any
Immed Post-Op	192	146 [76.0%]	25 [13.0%]	12 [6.3%]	9 [4.7%]	46 [24.0%]
Month 6	202	169 [83.7%]	10 [5.0%]	13 [6.4%]	10 [5.0%]	33 [16.3%]
Month 12	219	189 [86.3%]	10 [4.6%]	7 [3.2%]	13 [5.9%]	30 [13.7%]
Month 24	219	164 [74.9%]	24 [11.0%]	9 [4.1%]	22 [10.0%]	55 [25.1%]
Cumulative[1]	275	169 [61.5%]	49 [17.8%]	26 [9.5%]	31 [11.3%]	106 [38.5%]
Month 36	36	23 [63.9%]	6 [16.7%]	4 [11.1%]	3 [8.3%]	13 [36.1%]

Notes:
[1] Cumulative based on worst result over time up to Month 24.

Table 22:
Overall Interval Specific and Cumulative Summary of Any Finding of Acetabular or Femoral Radiolucency
Pivotal Study Unilateral Efficacy Cohort (Original Shell) {Investigator-based}

Interval	N	None	>0-1	>1-2	>2	Any
Immed Post-Op	221	208 [94.1%]	11 [5.0%]	1 [0.5%]	1 [0.5%]	13 [5.9%]
Month 6	229	214 [93.4%]	10 [4.4%]	3 [1.3%]	2 [0.9%]	15 [6.6%]
Month 12	243	214 [88.1%]	21 [8.6%]	5 [2.1%]	3 [1.2%]	29 [11.9%]
Month 24	229	174 [76.0%]	47 [20.5%]	4 [1.7%]	4 [1.7%]	55 [24.0%]
Cumulative[1]	288	215 [74.7%]	56 [19.4%]	11 [3.8%]	6 [2.1%]	73 [25.3%]
Month 36	169	123 [72.8%]	37 [21.9%]	5 [3.0%]	4 [2.4%]	46 [27.2%]

Notes:
[1] Cumulative based on worst result over time up to Month 24.

As noted in Tables 21 and 22, the use of independent radiographic results when defining success or failure in terms of the primary composite clinical success (CCS) endpoint did not significantly alter the results of the primary non-inferiority comparisons.

Health Related Quality of Life (HRQoL) (SF-12)

The Physical Component Summary (PCS) and Mental Health Component Summary (MCS) were determined from the SF-12, a well-known generic health-related quality of life instrument. Raw scores were converted to US population-based age and gender adjusted z-scores. These z-scores reflect percentile values with reference to the US population. Comparisons between the CONSERVE® Plus Pivotal Unilateral Efficacy cohort (Original Shell) and the respective cohorts for the TRANSCEND® Ceramic (C1) and TRANSCEND® Metal (C2) THR control devices are summarized in Table 23 below.

Table 23:
Descriptive Comparisons of Health-Related Quality of Life Age-Adjusted SF-12 PCS and MCS Z-Scores[1]
Summary Statistics Prior to Surgery, Month 24+, and Change Score by Device Group Pivotal Unilateral Efficacy Cohort (Original Shell) (I), Ceramic (C1), and Metal (C2) THR Unilateral Controls

			Pre-Surgery z-score			Month 24+[2] z-score			Change from Baseline		
SF-12	Device	N	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
SF-12 PCS z-score[3]	I	263	-1.82	1.19	-1.93	0.33	0.82	0.66	2.15	1.24	2.32
	C1	263	-1.88	1.09	-1.78	0.07	1.13	0.55	1.95	1.17	1.94
	C2	254	-1.85	1.18	-1.84	-0.03	1.20	0.40	1.82	1.29	1.96
SF-12 MCS z-score[4]	I	263	0.00	1.16	0.25	0.55	0.66	0.76	0.55	1.13	0.35
	C1	263	0.05	1.18	0.30	0.54	0.82	0.76	0.50	1.15	0.31
	C2	254	-0.01	1.10	0.10	0.43	0.89	0.72	0.43	1.21	0.31

Notes:
[1] Z-scores are age adjusted and reflect deviations from U.S. population age specific normative values contained in Tables 7.4 to 7.9 (pages 36 – 41) of the SF-12 scoring manual.
[2] Month 24+ values are from Month 24 or if Month 24 SF-12 was missing, from the first available subsequent values.
[3] PCS is the SF-12 Physical Component Score. Z-scores were computed by subtracting age specific normative mean values and then dividing by age specific normative standard deviations.
[4] MCS is the SF-12 Mental Health Component Score. Z-scores were computed by subtracting age specific normative mean values and then dividing by age specific normative standard deviations.

Preoperative mean PCS z-scores across CONSERVE® Plus (Group I), and TRANSCEND® Ceramic (Group C1) and TRANSCEND® Metal (Group C2) controls were approximately equivalent to the third (3rd) percentile values relative to US national normative data. This demonstrates that patients in all three device groups are at the lowest end of the normative physical spectrum and have profound physical deficits. At Month 24+, mean PCS z-scores increased in all Groups reflecting large improvements in physical HRQoL in all three groups. Controlling for baseline PCS z-scores, statistically significant differences were identified with respect to mean improvement at Month 24+ between CONSERVE® Plus and TRANSCEND® Ceramic (C1) ($p=0.003$) and CONSERVE® Plus and TRANSCEND® Metal (C2) ($p<0.001$).

Preoperative mean MCS z-scores across all Groups did not show mental deficits relative to the US national reference norms, as was the case with the physical scores. At Month 24+, however, improvement was still seen in mental scores for all Groups, but there were no significant differences between Groups.

Composite Clinical Success (CCS)

Table 24 provides the comparison of CCS between Groups based on various assumptions regarding follow-up interval definitions, imputations for HHS ROM/deformity scores, and radiographic review source. The highlighted row shows that 152 of 199 (76.4%) Pivotal Unilateral Efficacy cohort (Original Shell) procedures achieved Month 24+ CCS. In comparison, 153 of 202 (75.7%) procedures in the TRANSCEND® Ceramic (C1) Control Primary Efficacy cohort and 139 of 203 (68.5%) TRANSCEND® Metal (C2) Control Primary Efficacy cohort procedures achieved CCS at Month 24+. Non-inferiority of the investigational device relative to both control cohorts was demonstrated because the lower bound of the 95% confidence interval exceeded -0.08 (or -8%), which was the pre-specified margin of non-inferiority. Non-inferiority was also met in all other analysis cohorts.

Table 24:
Comparisons with THR Controls: Composite Clinical Success (CCS) at Month 24+[1]
For Different Assumptions Regarding Interval Definitions, Imputations, and Radiography Source

	Pivotal Unilateral Efficacy Cohort (Original Shell) (I)			Ceramic THR Control (C1)			Metal THR Control (C2)			I vs. C1		I vs. C2	
	n	N	Prop.	n	N	Prop.	n	N	Prop.	Diff.	95% CI LB[5]	Diff.	95% CI LB[5]
All evaluated[2] (Actual[B]), ROM/deformity imputaton[3], investigator radiography	211	270	0.781	197	260	0.758	175	249	0.703	0.024	-0.036	0.079	0.016
Within interval[4] (Actual[A]), ROM/deformity imputation[3], investigator radiography	194	252	0.770	153	202	0.757	139	202	0.688	0.012	-0.054	0.082	0.013
All evaluated[2] (Actual[B]), ROM/deformity imputation disabled, investigator radiography	208	267	0.779	197	260	0.758	174	246	0.707	0.021	-0.039	0.072	0.008
Within interval[4] (Actual[A]), ROM/deformity imputation disabled, investigator radiography	190	248	0.766	153	202	0.757	139	203	0.685	0.009	-0.058	0.081	0.012
Within interval[4] (Actual[A]), ROM/deformity imputation disabled, independent radiography	152	199	0.764	153	202	0.757	139	203	0.685	0.006	-0.064	0.079	0.006

Notes:

[1] For Month 24+ CCS, missing Month 24 endpoints were replaced by endpoints from subsequent evaluations if available.

[2] WMT defined All Evaluated (Actual[B]) intervals as follows: Pre-op< 0 days post surgery; Immed. interval 1-45 days; 6 Mo. Interval 46-210 days; 1 Yr Interval 211-425 days; 2 Yr Interval 426-790 days.

[3] ROM/deformity imputations. When Harris Hip Scores were otherwise complete, missing ROM was set to 0 of 5 points and/or missing deformity was to 0 of 4 points, reducing the maximum HHS to 95, 96, or 91 (when both were missing) points.

[4] Within interval (Actual[A]) analyses based on Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications Document issued on: December 2, 2004.[6] The 2 Yr interval is (24+/-2 mo.).

[5] Lower bounds of 1-sided 95% confidence intervals for true differences between Conserve Plus and the control groups. The study was designed to demonstrate clinical non-inferiority defined as a success rate that was, at most, 0.08 less than control.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

CDRH determined that the applicant provided an adequate device description and the preclinical mechanical bench testing provides a reasonable assurance of device safety.

A prospective, multi-center, historically controlled Investigational Device Exemption (IDE) study was conducted using components of the CONSERVE® Plus Total Resurfacing Hip System in the United States. *A priori* objectives were used to demonstrate non-inferiority to historical control groups in terms of a Month 24+ composite clinical success (CCS) criterion. The historical control groups were derived from the regulatory studies for the TRANSCEND® Ceramic IDE and the TRANSCEND® Metal IDE.

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The most commonly reported adverse events related to the CONSERVE® Plus Total Resurfacing Hip System device were femoral neck fracture, component migration/loosening, femoral subsidence, dislocation, infection, impingement, and trochanteric fracture. Among the All Enrolled Audited procedures cohort, 67 of 1366 (4.9%) CONSERVE® Plus procedures, 29 of 963 (3.0%) TRANSCEND® Ceramic (C1) controls, and 20 of 388 (5.2%) TRANSCEND® Metal (C2) controls experienced at least one complication assessed by the DSMB as severe and further assessed as possibly, probably, or definitely device-related. There was a statistically significantly higher complication rate for the CONSERVE® Plus device as compared to the TRANSCEND® Ceramic (C1) control (Fisher's exact test p=0.026). In contrast, there was no statistically significant difference between CONSERVE® Plus and TRANSCEND® Metal control (C2) (Fisher's exact test p=0.79). Additional analyses on the other safety endpoints that had statistically significant differences as compared to the control groups were performed and it was concluded that they were not clinically significant.

In addition, the safety of the CONSERVE® Plus Total Resurfacing Hip System was evaluated in terms of device revision and corresponding risk factors, survivorship, and metal ions. As reported in the Summary of Primary Clinical Study section (Section X), the rates of revision between the investigational cohorts and historic controls were comparable if not slightly higher for CONSERVE® Plus. The associated risk factors, as determined from data collected as part of the clinical study and retrieval analysis, were found to pertain to surgical training and technique, and/or patient selection. Therefore, obtaining adequate surgeon training, and consideration of these surgical technique and patient selection risk factors may help decrease the need for device revision. For a complete list of risk factors, please refer to the device labeling.

Among patients in the All Enrolled Audited CONSERVE® Plus procedures, there was no statistically significant difference in survival distributions between CONSERVE® Plus and TRANSCEND® Metal (C2) controls at two years (log-rank p=0.30) or based on all available follow-up (log-rank p=0.42). In contrast, survival distributions were

significantly lower for the CONSERVE® Plus device as compared to the TRANSCEND® Ceramic (C1) control at two years (log-rank p=0.004) as well as based on all available follow-up (p=0.02). Among patients in the Pivotal Unilateral Efficacy Cohort (Original Shell), there were no statistically significant differences in survival rates between groups.

Regarding metal ions, although there have been literature reports of asymptomatic pseudotumor and delayed hypersensitivity reaction (ALVAL) in some patients which may be associated with abnormal wear, metal hypersensitivity or toxic effects and while the concentration of metal ions will be higher in patients who receive metal-on-metal hip implants versus patients who receive other bearing surfaces (i.e., metal-on-polyethylene, ceramic-on-ceramic), in the vast majority of patients there has been no direct evidence demonstrating that elevated metal ion levels adversely effect health.

B. Effectiveness Conclusions

Effectiveness was evaluated via a Composite Clinical Success endpoint that included an evaluation of pain and function using the Harris Hip Score (HHS), radiographic data, survivorship, and a safety assessment for the occurrence of a serious, device-related adverse event. It also included a patient self-evaluation of health related quality of life which included physical and mental-health components (SF-12). In a comparison of the Composite Clinical Success Criterion between the investigational and control groups, non-inferiority of the investigational device relative to both historical control cohorts was demonstrated.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on November 3, 2009. The final conditions of approval cited in the approval order are described below.

The sponsor has agreed to conduct the following two post-approval studies:

1. Longer-Term Study: This study is designed to evaluate the longer term safety and effectiveness of the CONSERVE Plus Total Resurfacing Hip System. Specific study questions to be answered are: (1) What is the longer-term safety performance of the CONSERVE Plus Total Resurfacing Hip System? (2) What is the longer-term effectiveness performance of the CONSERVE Plus Total Resurfacing Hip System? A single-arm, multi-center, prospective cohort study design with hypothesis testing will be used to determine the 10-year (120-month) survivorship and pain and function levels, as determined using the Harris Hip Score, using the CONSERVE Plus Total Resurfacing Hip System. Patients to be

recruited in the longer-term study will include those who were previously enrolled in the CONSERVE Plus Total Resurfacing Hip System investigational device exemption (IDE) study, G990328; are part of the All Enrolled Unilateral Cohort (original shell) as described in PMA P030042, with the exception of the four investigational sites identified in the sponsor's draft protocol; meet the inclusion/exclusion criteria outlined in the draft protocol; and, have not previously undergone device removal/revision. The study population will consist of this same cohort of patients, but also include those who have undergone device revision/removal, with at least 229 CONSERVE Plus Total Resurfacing Hip System patients followed through the 10-year post-operative visit. To minimize patient selection bias, the sponsor has agreed to take reasonable measures to recruit all eligible patients and will document the reasons for why patients are not enrolled. The sponsor has also agreed to take reasonable measures to avoid loss to follow-up and will document the reasons why patients are lost to follow-up. If the follow-up rate is unacceptably low during the 10-year follow-up, FDA will consider other regulatory options to limit loss-to-follow-up, including requiring the sponsor to recruit more subjects. Clinical success at 120 months post-operative for each patient will be survivorship, defined as freedom from revision or removal; and, at least "good" function/pain relief defined as a Harris Hip Score ≥ 80. Secondary endpoints, also assessed at 120 months post-operatively, include: radiographic outcome, metal ion concentration, renal function (BUN, creatinine, and GFR), patient satisfaction as assessed by the SF-12 and safety endpoints (device-related adverse events at 120 months post-operative). Safety data will also be collected throughout the study, including but not limited to: all adverse events, including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome, reported for these patients. Patients will undergo clinical and radiographic evaluation postoperatively at years 5, 8 and 10. Patients will receive a mailed questionnaire to evaluate pain, function, and patient satisfaction at years 6, 7, and 9. Patients will also have serum levels of cobalt and chromium ions and renal function data collected at 5, 8, and 10 years post-operatively.

The sponsor has agreed to submit post-approval study reports, separately for this study, every six months for the first two years and then annually until the study is completed. The sponsor must also update their patient and physician labeling (via PMA supplement) to reflect the 5- and 10-year findings of the longer-term study as soon as these data are available, as well as any other time point deemed necessary by FDA if significant new information from the study becomes available.

2. New Enrollment Study: This study is designed to examine the performance of the CONSERVE Plus Total Resurfacing Hip System in newly enrolled patients under real world conditions of use. The specific question to be answered is: What is the performance of the CONSERVE Plus Total Hip Resurfacing system under actual conditions of use? A multi-center, prospective, historically controlled cohort study design with hypothesis testing will be used to determine the 2-year (24-month) survivorship and pain and function levels, as determined using the Harris

Hip Score, using the CONSERVE Plus Total Hip Resurfacing System. The sponsor has agreed to recruit 4 new clinical sites with a geographically diverse mix of academic, referral, and/or community based sites; and, investigators with different levels of experience using hip resurfacing devices. The sponsor has agreed to enroll 183 new study subjects and follow them for 2 years, with a minimum of 155 study subjects followed through the 2- year follow-up visit. The sponsor has agreed to take reasonable measures to limit cumulative loss-to-follow-up and will document the reasons why patients are lost to follow-up. If the follow-up rate is unacceptably low during the 24 month follow-up, FDA will consider other regulatory options to limit loss-to-follow-up, including requiring the sponsor to recruit more subjects. Clinical success at 24 months post-operative for each patient will be survivorship, defined as freedom from revision or removal; and, at least "good" function/pain relief defined as a Harris Hip Score ≥ 80. The secondary endpoints, also assessed at 24 months, include: SF-12 (MCS & PCS scores), radiographic components (Cup Position, Cup inclination, Cup Migration, Femoral Position, Femoral Angulation, Femoral subsidence, and Acetabular and Femoral Radiolucencies), Metal Ions (Serum Cobalt and Serum Chromium), Renal Function (GFR, Creatinine, and BUN); and safety endpoints (device-related adverse events at 24 months). Safety data will also be collected throughout the study, including but not limited to: all adverse events, including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome, reported for these patients. Patients will undergo clinical and radiographic evaluation pre-operatively and postoperatively at 0-60 days, 12 and 24 months. Patients will also have serum levels of cobalt and chromium ions and renal function data collected pre-operatively and at 12 and 24 months post-operatively.

The sponsor has agreed to submit post-approval study reports, separately for this study, every six months for the first two years and then annually until the study is completed. The sponsor must also update their patient and physician labeling (via PMA supplement) to reflect the 2-year findings of the post-approval study in newly enrolled subjects as soon as these data are available, as well as any other time point deemed necessary by FDA if significant new information from the study becomes available.

The sponsor has also agreed to the following conditions of approval:

3. The sponsor has agreed to implement a training program, as outlined in the PMA. The training program includes quarterly investigator teleconferences or meetings for the first two years of the New Enrollment study to provide a clinical update to investigators; to discuss study issues including adverse events; and to identify recommendations for improvement of the training program or labeling. If some investigators cannot attend the conference, the sponsor has agreed that these investigators will be contacted by telephone or will be sent a feedback form so that individual feedback can be obtained. The sponsor has agreed to submit a

summary of the minutes of the quarterly teleconferences/ physical meeting/ investigator feedback information as part of the PAS Interim Reports.

The sponsor has agreed that the results of the post-approval studies and training program assessment outlined in items 1-3 above must be reflected in the labeling (via a supplement) when the post-approval study is completed, and/or at earlier timepoints, as needed.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

[1] ASTM F75: Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

[2] *Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement*, dated April 28, 1994.

[3] ISO 21535: Non-active surgical implants – Joint replacement implants - Specific Requirements for hip-joint replacement implants.

[4] ISO 11137: Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization.

[5] ASTM F1377: Standard Specification for Cobalt-28 Chromium-6 Molybdenum Powder for Coating of Orthopedic Implants (UNS R30075)

[6] Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications, December 2, 2004.

[7] Peto T, Pike MC, Armitage P, Breslow NE, Cox DR, Howard V, Mantel N, McPherson K, Peto J, and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II: Analysis and examples. *British Journal of Cancer*, **35**:1-39, 1977.

[8] Kaplan EL and Meier P. Nonparametric estimation from incomplete observations, *Journal of the American Statistical Association*, **53**:45 7-481, 1958.

[9] Skipor, *et al.*, in, "Serum and urine metal levels in patients with metal-on-metal surface arthroplasty," *J Mat Sci Mat Med* 13 (2002), p.1227-34.

[10] "Metal Ion Levels In Asymptomatic Pseudotumours Associated With Metal-on-metal Hip Resurfacings." Kwon, et. al. Paper No. 44, *55th Annual Meeting of the Orthopaedic Research Society, Las Vegas, 2009.*